

Protocol Number: HLAB - 001

Human Laboratory Study of Varenicline for Alcohol Use Disorder

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DATE: November 3, 2017

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 312)
- International Conference on Harmonisation (ICH) E6

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

1. Protocol Synopsis

Name of Sponsor/Company: National Institute on Alcohol Abuse and Alcoholism (NIAAA)	
Name of Investigational Product: Varenicline tartarate	
Name of Active Ingredient: Varenicline tartarate	
Protocol Number: HLAB-001	
Study Title: Human Laboratory Study of Varenicline for Alcohol Use Disorder	
NIAAA Principal Investigator: Raye Litten, Ph.D.	
Study Centers: 2 sites in the United States	
Study Period: Estimated date first subject enrolled: March 1 st , 2017 Estimated date last subject completed: January 1 st , 2018	Phase of Development: 1b
<p>Objectives:</p> <p>Primary: The primary objective of this study is to evaluate the effect of varenicline 1 mg twice-daily (BID), compared with matched placebo, on alcohol cue-elicited alcohol craving during a human laboratory paradigm after two weeks of BID daily dosing among subjects with moderate alcohol use disorder (AUD) as confirmed by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5™).</p> <p>Secondary: Secondary objectives include evaluation of varenicline compared with placebo on reduction of alcohol consumption, alcohol craving, cigarette smoking (among smokers) and nicotine use (among nicotine users), mood, sleep, study retention, and safety and tolerability throughout the last 4 weeks of the maintenance phase of the study.</p>	
<p>Methodology: This study is a double-blind, randomized, placebo-controlled, parallel group, two-site study designed to assess the effects of varenicline as compared with placebo on responses to <i>in vivo</i> alcohol cue exposure in the human laboratory setting. After signing informed consent, subjects will be screened for eligibility including medical history, physical examination, vital signs, electrocardiogram (ECG), drinking history by the timeline follow-back (TLFB) method, alcohol breathalyzer test, Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA), medication use, MINI neuropsychiatric interview, urine toxicology screen, clinical chemistry, response to cue reactivity, and Columbia Suicide Severity Rating Scale (CSSR-S). Women of child-bearing potential will have a pregnancy test. If eligible for the study, subjects will be randomized using a stratified permuted block randomization procedure in an approximate 1:1 ratio (targeting 24 subjects per group – 12 subjects per group per site) to receive either varenicline or placebo for 6 weeks. Any nicotine use versus no use (cigarettes, cigars, chewing tobacco, electronic cigarettes, etc.) in the week before randomization is the stratification variable.</p> <p>Varenicline or matched placebo will be titrated over the first week of the study up the maintenance dose of 1 mg (active) or two capsules (placebo) taken orally BID for an additional 5 weeks. Subjects will be seen in the clinic at screening, at randomization and 6 other times during the study. A final follow-up telephone interview will occur during Week 9 (2 weeks after the end of study visit).</p> <p>After the first two weeks and after five weeks of investigational product administration at Study Week 3 and Study Week 6, respectively, subjects will undergo a cue reactivity paradigm session (HLAB) including 4 individual visual analog scale (VAS) items assessing alcohol craving, 2 VAS items assessing emotional reactivity to picture stimuli, and 2 items assessing emotional manipulation. Immediately after the HLAB session, subjects will view each picture again and record the emotion felt using the Self-Manikin Assessment (SAM). Other assessments at baseline (prior to the first dose of investigational product) and/or during the maintenance period include clinical chemistry, mood/behavior/thinking questions, blood for medication compliance, vital signs, ECG, concomitant medications, CIWA-AR, pregnancy test and birth control methods, drinking goal, adverse events (AEs), Alcohol Craving Questionnaire – Short Form (ACQ-SF-R), Penn Alcohol Craving Scale (PACS), Fagerström Test for Nicotine Dependence, smoking quantity/frequency, Pittsburg Sleep Quality Index (PSQI), and Profile Of Moods State (POMS).</p>	

Number of Subjects (Planned): 48			
Main Inclusion/Exclusion Criteria: Subjects will be male and female at least 21 years of age with 4 or more DSM-5™ symptoms of AUD (moderate to severe AUD). They must also be seeking treatment for alcohol dependence and if male, report drinking an average of 35 drinks per week or if female report drinking an average of 28 drinks per week prior to consent. A “heavy drinking day” is 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men.			
Investigational Product, Dosage and Mode of Administration: Dose titration, maintenance and taper will occur as scheduled below. The target maintenance dose is 1.0 mg BID. Subjects in the placebo group will take an equivalent number of placebo capsules. Both the varenicline and placebo capsules will be encapsulated to protect the study blind.			
Study Period	Time Period	AM Dose (# of capsules)	PM Dose (# of capsules)
Titration	Week 1, Days 1-3	0.5 mg (1)	None
Titration	Week 1, Days 4-7	0.5 mg (1)	0.5 mg (1)
Maintenance	Weeks 2-6	1.0 mg (2)	1.0 mg (2)
Reference Therapy, Dosage and Mode of Administration: Identically over encapsulated placebo tablets will be administered according to the same schedule as the varenicline capsules.			
Duration of Study: Each subject will participate in the study for up to 10 weeks, including up to 2 weeks of screening, 6 weeks of treatment, one end-of-study visit, and a final telephone contact 2 weeks after completing treatment.			
Criteria for Evaluation: Primary: The primary efficacy endpoint is difference between the varenicline and placebo groups on the alcohol craving Visual Analog Scale (VAS) summary score (and subscales) in response to the alcohol cue reactivity human laboratory paradigm. Confirmatory endpoints for the human laboratory paradigm session include: VAS items assessing beverage preference and emotional responsivity to the pictures. Secondary: Secondary efficacy endpoints will be analyzed over the last 4 weeks of the maintenance phase of treatment. <ol style="list-style-type: none"> 1. Percentage of subjects with no heavy drinking days. A “heavy drinking day” is 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men. 2. Percentage of subjects abstinent from alcohol 3. Percentage of subjects with at least a World Health Organization (WHO) 2-level decrease in alcohol consumption 4. Percentage of subjects with at least a WHO 1-level decrease in alcohol consumption 5. Percentage of days abstinent per week 6. Percentage of heavy drinking days per week 7. Percentage of very heavy drinking days per week. A “very heavy drinking day” is 8 or more drinks per drinking day for women and 10 or more drinks per drinking day for men. 8. Weekly mean number of drinks per week 9. Weekly mean drinks per drinking day 10. Cigarettes smoked per week among smokers 11. Percentage of subjects with no nicotine use among nicotine users 12. Alcohol craving score (PACS) 13. Sleep quality (PSQI) score 14. Profile of Mood States (POMS) score Safety Endpoints: Safety endpoints will be analyzed over the entire treatment and follow-up period.			

1. Vital signs
2. Blood chemistries
3. BAC by breathalyzer
4. Urine drug tests
5. AEs
6. ECG results
7. CIWA-AR scores
8. Frequency of subjects with suicidal ideation at any time during the treatment period (C-SSRS)
9. Neuropsychiatric safety variables: Mood changes, Behavior/Thinking changes, increased intoxicating effect of alcohol
10. Concomitant medication use
11. ACQ-SF-SR

Compliance: Self report of compliance with investigational products and varenicline plasma levels.

Statistical Methods (Data Analysis):

Analysis Populations:

Modified intention-to-treat (mITT) Analysis Set: The mITT set is defined as subjects randomized to participate in the study that took at least one dose of investigational product and had at least one non-missing VAS craving primary endpoint (completed human laboratory assessment).

Evaluable Analysis Set: The evaluable analysis set for the secondary endpoints is defined as those subjects randomized to the study who took at least 1.5 mg per day for at least 80% of days in Weeks 2-6. All evaluable analysis sets will exclude subjects with a major protocol deviation.

Analysis of the Primary Efficacy Endpoint: Repeated-measures mixed effects models will be used to examine drug-placebo differences in VAS craving ratings in response to beverage exposure, where drug is treated as a fixed, between-subjects variable and beverage presentation is the repeated measure. Beverage will be considered a fixed, within-subjects variable and subject as a random effect.

Analysis of the Secondary Endpoints: Continuous secondary endpoints (percent heavy drinking days, percent very heavy drinking days, percent days abstinent, drinks per week, drinks per drinking day, number of cigarettes smoked per week, PACS, POMS, and PSQI score) will be analyzed using a mixed-model repeated measures ANCOVA controlling for site, nicotine use in the week before randomization, and baseline drinking as fixed factors. Models will also include time by treatment group interaction term. Additional covariates may be included that are significantly correlated with outcome and/or if there are differences across the treatment groups.

Analysis of the dichotomous secondary endpoints (percentage subjects with no heavy drinking days, percentage subjects abstinent from alcohol, percentage of subjects achieving at least a one and two-level shift in WHO alcohol consumption, and percentage of subjects with no nicotine use over the last 4-weeks of maintenance period among subjects with any use during the week before randomization) will be conducted via logistic regression. Covariates may be included provided there are a sufficient number of events.

In general, no imputation for missing endpoint data will be performed. However, as a sensitivity analysis, missing drinking data for the secondary endpoint percent heavy drinking days will be handled in two ways as done by [Litten et al \(2013\)](#): (a) by imputing missing data as heavy drinking days; and (b) by using multiple imputation. The multiple imputation model will the same covariates as the efficacy model for this endpoint. Twenty-five iterations of this model will be run, and model estimates will be averaged using PROC MIANALYZE in SAS, or a similar procedure.

Safety Analyses:

AEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, and class (SOC) designation. The severity, frequency, and relationship of AEs to investigational product will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on preferred terminology) will be counted once only for a given study subject. If the same AE occurred on multiple occasions, the highest severity will be assumed. Thus, study participants are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE. Laboratory data, pregnancy test results, and alcohol breathalyzer results, psychiatric symptoms, and CIWA scores will be reported

as summary statistics. The numbers and proportion of subjects who reported CIWA scores ≥ 10 at any time after the start of dosing will be presented. ACQ-SF-R will be administered before and after exposure to alcohol and picture stimuli during the cue reactivity paradigm on the screening visit and study week 3 visit to ensure that subjects have returned to baseline levels.

Compliance and Participation Outcomes: Medication compliance is defined as the amount of medication taken as a proportion of the total amount prescribed. Compliance will also be evaluated by determining the proportion of subjects who were prescribed varenicline, reported taking varenicline, and had a plasma sample with detectable varenicline. The participation rate is the percentage of subjects with complete drinking data. Compliance and participation rates will be reported on a weekly basis and across the entire trial duration

Baseline Descriptive Statistics: Summaries of the characteristics of the subjects in each of the study groups at baseline will be prepared for both the mITT and evaluable analysis sets. Baseline characteristics will be compared between the varenicline and placebo groups using appropriate statistical methods.

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3. List of Abbreviations and Definition of Terms

Abbreviation	Definition
ACQ-SF-R	Alcohol Craving Questionnaire – Short Form – Revised
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUD	Alcohol Use Disorder
BAC	Blood alcohol concentration
BID	Twice daily
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act
CIWA-AR	Clinical Institute Withdrawal Assessment for Alcohol-revised
CrCl	Creatinine clearance
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case Report Form
CTCAE	Common terminology criteria for adverse events
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EM	Emotional Manipulation
EOS	End of study
EtG	ethylglucuronide
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HIPAA	Health Insurance Portability Accountability Act
hr	Hour
ICH	International Conference on Harmonization
IRB	Institutional Review Board
L	Liter
MAOI	Monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
µg	Microgram
min	Minutes
MINI	MINI Neuropsychiatric Interview
mITT	Modified intention-to-treat
mL	Milliliter

Abbreviation	Definition
mm	Millimeter
NIAAA	National Institutes on Alcohol Abuse and Alcoholism
OTC	Over-the-counter
oz	Ounce
PACS	Penn Alcohol Craving Scale
PI	Principal Investigator
PK	Pharmacokinetic
POMS	Profile of Mood State
PSQI	Pittsburg Sleep Quality Index
PT	Preferred Term
SAE	Serious adverse event
SAM	Self-Assessment Manikin
SAP	Statistical analysis plan
SD	Standard deviation
SDU	Standard drinking unit
SOC	System Organ Class
SNRI	Serotonin-norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
THC	Tetrahydrocannabinol
TLFB	Timeline followback
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
WHO	World Health Organization

4. Introduction

4.1. Alcohol Use Disorder

Alcohol use disorder (AUD) (alcohol dependence and abuse) affects 76 million adults world-wide, including 18 million Americans, and is responsible for a myriad of medical, psychological, social, economic and personal problems ([Litten et al-2012](#)). Tragically, more than 2.5 million individuals including 80,000 Americans die each year from alcohol-related events. The total economic cost to society is a staggering \$224 billion each year in the United States (US) ([NIAAA-2014](#))

4.2. Human Laboratory Studies

Human laboratory studies of acute responses to alcohol, alcohol cues, or other pharmacological and/or experimental manipulations have progressed in important ways, and have the potential to greatly advance our understanding neurobehavioral mechanisms of alcohol effects on behavior ([Plebani et al-2014](#)). These studies may help identify important individual difference factors affecting alcohol response, such as personal traits, drinking characteristics, and genotype, and aid in our understanding of the variability in cue and craving states, and provide additional information relevant to the design of clinical studies to assess the effectiveness of pharmacological agents. The study to be conducted in this protocol utilizes an alcohol cue reactivity model to attempt to recreate in the laboratory risk conditions for relapse similar to those experienced by alcoholics in their natural environment ([Niaura et al-1988](#); [Litt and Cooney- 1999](#)).

Human laboratory studies have been conducted that examine the effect of positive and negative affective stimuli and beverage cues on craving in non treatment-seeking subjects with alcohol dependence. In a study reported by [Mason et al \(2008\)](#), the moderating effects of a priming exposure to both positive and negative affective stimuli on beverage cue-induced craving were examined. Subjects were exposed to a standardized set of pleasant, neutral, or unpleasant visual stimuli followed by alcohol or water cues and psychophysiological cue reactivity measures were obtained during beverage presentation and subjective reactivity measures were taken following beverage presentation. Psychophysiological measures included heart rate, skin conductance, and facial electromyogram (EMG) which were monitored throughout each experimental trial as confirmatory measures of the primary subjective measures of craving and emotion. Assessment of alcohol craving in response to each affect-beverage condition was assessed using four individual Visual Analog Scales (VAS). In addition, the Self-Assessment Manikin (SAM) ([Bradley and Lang-1994](#)) was utilized as a non-verbal pictorial assessment technique to measure emotional reactivity (valence, arousal, and dominance) associated with a person's affective reaction to stimuli.

Results of mixed-effect analyses of subjective outcome measures in the [Mason et al \(2008\)](#) study showed statistically significant main effects of alcoholic beverage cue on three of four individual craving questions, and on the mean of the four items. The effect size for alcoholic beverage cue on subjective craving measures ranged from 0.58 (strength of craving), to 0.22 (difficult to turn down); the composite effect size was 0.45. Positive affect independent of beverage cue significantly increased craving strength and showed a trend for a significant increase in the composite craving scale. Effect sizes for positive affect ranged from 0.55 (difficult to turn down)

to nearly zero (make things perfect). For negative affect, the largest effect size was 0.18 (strength of craving), and none of the effects of negative affective stimuli on measure of craving were statistically significant. No interaction effects were detected between alcoholic beverage cue and affective stimuli on any outcome measure of craving. An important finding of this study is that positive affective stimuli commonly associated with drinking situations can induce craving in the absence of alcohol cues.

Another human laboratory proof-of-concept study was conducted by [Mason et al \(2009\)](#) to evaluate the effectiveness of gabapentin to attenuate some of the symptoms of protracted abstinence from alcohol. The laboratory study design was intended to model and predict the critical first week on medication during a clinical trial, when participants' sleep and mood disturbances, or other side effects, could dramatically affect medication compliance and increase the risk for subject discontinuation. The experimental design mirrored the human lab study model where positive affective stimuli induced induce craving ([Mason et al-2008](#)). This study design employed a 4-hour cue reactivity protocol which included a baseline evaluation, followed by the cue reactivity procedures, and subsequent debriefing. As in the previous human lab study, 3 affective stimuli (positive, neutral, negative) and 2 beverage cues (alcohol and water) were deployed within-subjects, in a block-factorial design of 6 repeated measures. All six mood-beverage cue combinations were presented to each subject (with order varying systematically across subjects) during the course of a single afternoon. Alcohol craving was assessed using four separate VAS measurements and psychophysiological measures of heart rate, skin conductance, and EMG were recorded.

This study results showed that subjects randomized to receive gabapentin had significantly attenuated craving responses to three of the four subjective craving measures (how strong is your urge to drink, I would drink now if I could, it would be difficult to turn down a drink now) [Mason et al \(2009\)](#). In contrast, gabapentin reduced arousal induced by all three types of cues (beverage, positive affect, and negative affect) as measured by SAM emotional reactions. Given that subjects randomized to receive gabapentin had reduced alcohol craving, and analysis of the secondary study endpoints demonstrated significantly improved measures of sleep quality, the hypothesis was supported that gabapentin may be effective for treating the protracted abstinence phase in alcohol dependence.

4.3. Rationale for Studying Varenicline

Both nicotine and alcohol have been shown to stimulate nicotinic acetylcholine receptors which elevate dopamine levels in the nucleus accumbens, an important part of the brain reward system ([Tizabi et al-2002](#)). These studies supported the hypothesis that administration of selective nicotinic antagonists may be of therapeutic potential in reducing the rewarding effects of ethanol. Separate administration of varenicline or ethanol produced significant elevations of dopamine compared with saline injections, and when the two drugs were administered concomitantly, they counteracted each other's dopamine enhancing properties ([Erickson et al-2009](#)). The comparability of doses needed to inhibit alcohol-related biochemical changes and behavior to nicotinic processes suggests that the regimen used clinically to diminish nicotine craving might also diminish alcohol craving.

In a human lab study, varenicline's effects (2 mg/day vs. placebo) on alcohol self-administration using an established laboratory paradigm in non-alcohol-dependent heavy drinkers (n=20) who

were daily smokers was investigated ([McKee et al-2009](#)). Following 7 days of medication pretreatment of placebo or varenicline (0.5 mg daily for Days 1 and 2, 0.5 mg twice daily for Days 3–5, and 1.0 mg twice daily on Days 6 and 7), participants were first administered a priming dose of alcohol (0.3 g/kg) and subjective and physiologic responses were assessed. A 2-hour alcohol self-administration period followed during which participants could choose to consume up to 8 additional drinks (each 0.15 g/kg). Varenicline significantly reduced the number of drinks consumed compared to placebo and increased the likelihood of abstaining from any drinking during the self-administration period. Following the priming drink, varenicline attenuated alcohol craving and reduced subjective reinforcing alcohol effects (high, like, rush, feel good, intoxicated). AEs associated with varenicline were minimal and, when combined with alcohol, produced no significant effects on physiologic reactivity, mood, or nausea.

Varenicline significantly reduced alcohol consumption and craving in a multisite, Phase 2 double-blind, placebo controlled randomized study suggesting that varenicline may be a potentially viable option for the treatment of alcohol use disorders (AUD) ([Litten et al-2013](#)). Results of this study demonstrated that the varenicline group experienced significantly lower weekly percent heavy drinking days than the placebo group (37.9 vs. 48.4, respectively; $p=0.03$; $d=0.31$). In addition, it was shown that the varenicline group had fewer drinks per day and lower percent of very heavy drinking days than the placebo group (p 's <0.05). In addition, the varenicline group scored lower on alcohol craving as measured by the Penn Alcohol Craving Scale (PACS), a five-item self-administered instrument for assessing craving ([Flannery et al-1999](#)).

4.4. Discussion of the Study Design

The current study design will utilize repeated-measures mixed effects models to assess the varenicline-placebo differences in Visual Analog Scales (VAS) craving ratings. The design includes 3 affective image (positive, neutral, negative affect) and 2 beverage (alcohol, water) within-subjects conditions where drug is treated as a fixed between-subjects variable, beverage condition is the fixed within-subjects repeated measure, and subject is the random effect. All six mood-beverage cue combinations will be presented to each subject (with order varying systematically across subjects) during the course of a single afternoon. Since order effects of cue presentation have been observed in previous studies, subjects will be systematically assigned one of six cue order combinations, in the order they were enrolled in the study.

To verify a safe return to a baseline state following the cue exposure trials, the Alcohol Craving Questionnaire short form revised (ACQ-SF-R) ([Singleton et al-1994](#)) will be administered both prior to and following the cue reactivity procedure to ensure that the trials had not resulted in a prolonged subjective urge to drink.

5. Study Objectives

5.1. Primary Objective

The primary objective of this study is to evaluate the effect of varenicline 1 mg twice-daily (BID), compared with matched placebo, on alcohol cue-elicited alcohol craving during a human laboratory paradigm after two weeks of BID daily dosing among alcohol treatment-seeking subjects with moderate to severe alcohol use disorder (AUD) as confirmed by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5™).

5.2. Secondary Objectives

Secondary objectives include evaluation of varenicline compared with placebo on reduction of alcohol consumption, alcohol craving, cigarette smoking (among smokers), nicotine use (among nicotine users), mood, sleep, study retention, and safety and tolerability throughout the last 4 weeks of the maintenance phase of the study.

6. Investigational Plan

This study is a double-blind, randomized, placebo-controlled, parallel group, two-site study designed to assess the effects of varenicline as compared with placebo on responses to in vivo alcohol cue exposure in the human laboratory setting. After signing informed consent, subjects will be screened for eligibility including medical history, physical examination, vital signs, electrocardiogram (ECG), drinking history by the timeline follow-back (TLFB) method, alcohol breathalyzer test, Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA), medication use, Mini neuropsychiatric interview, urine toxicology screen, clinical chemistry, response to water cue craving session, and Columbia Suicide Severity Rating Scale (CSSR-S). Women of child-bearing potential will have a pregnancy test. If eligible for the study, subjects will be randomized using a stratified permuted block randomization procedure in an approximate 1:1 ratio (targeting 24 subjects per group – 12 subjects per group per site) to receive either varenicline or placebo for 6 weeks. Any nicotine use versus no use (cigarettes, cigars, chewing tobacco, electronic cigarettes, etc.) over the past week prior to randomization is the stratification variable.


Varenicline (1 mg) or matched placebo will be taken orally BID for 6 weeks. Subjects will continue taking medication for an additional 4 weeks following the human lab paradigm. Subjects will be seen in the clinic at screening, at randomization and 6 other times during the study. A final follow-up telephone interview will occur during Week 9 (2 weeks after the end of study visit).

After the first two weeks of investigational product administration and after five weeks at Study Week 3 and Study Week 6, respectively, subjects will undergo a cue reactivity paradigm session (HLAB) including 4 individual visual analog scale (VAS) items assessing alcohol craving and emotional reactivity. Immediately after the HLAB session, subjects will view each picture again and record the emotion felt using the Self-Manikin Assessment (SAM). Other assessments at baseline (prior to the first dose of investigational product) and/or during the maintenance period include clinical chemistry, mood/behavior/thinking questions, blood for medication compliance, vital signs, ECG, concomitant medications, CIWA-AR, pregnancy test and birth control methods, drinking goal, adverse events (AEs), Alcohol Craving Questionnaire – Short Form (ACQ-SF-R), Penn Alcohol Craving Scale (PACS), Fagerström Test for Nicotine Dependence, smoking quantity/frequency, Pittsburg Sleep Quality Index (PSQI), Medication Adherence Questionnaire (MAQ), Self-report Habit Index (SRHI) and Profile Of Moods State (POMS).

Study assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments ([Table 1](#)).

Table 1: Schedule of Assessments

			Maintenance						F/U Call
	Screening	Titration Randomization		HLAB			HLAB	EOS Visit	
Clinic Visit #	1	2	3	4	5	6	7	8	PHONE
Study Week	-2 to -1	1	2	3	4	5	6	7	9
Informed Consent	X								
Alcohol Breathalyzer	X	X	X	X	X	X	X	X	
Urine Drug Screen ^a	X	X	X	X	X	X	X	X	
Locator Form	X	Update	Update	Update	Update	Update	Update	Update	
Demographics	X								
Medical History	X	Update							
Physical Exam (and weight)		X							
MINI V 7.0	X								
Clinical Chemistry ^b	X			X				X	
Hematology	X								
Mood/Behavior/Thinking Questions		X	X	X	X	X	X	X	
Eligibility Checklist	X	X							
Blood for medication compliance				X				X	
Vital Signs ^c	X	X	X	X	X	X	X	X	
ECG	X							X	
Prior and Concomitant Meds	X	X	X	X	X	X	X	X	X
CIWA-AR	X	X	X	X	X	X	X	X	X
Drug compliance/ accountability		Dispense - Titration	X	X	X	X	X	X	
Pregnancy Test + birth control	X	X	X	X		X		X	
Drinking Goal		X							
Cue Reactivity Paradigm - Screen Visit - VAS craving, EM	X								
AEs		X	X	X	X	X	X	X	X

			Maintenance						F/U Call
	Screening	Titration Randomization		HLAB			HLAB	EOS Visit	
Clinic Visit #	1	2	3	4	5	6	7	8	PHONE
Study Week	-2 to -1	1	2	3	4	5	6	7	9
C-SSRS		X	X	X	X	X	X	X	
RANDOMIZATION		X							
Brief Telephone Interview ^d		Week 1, Day 3 and Day 7	4 days prior to HLAB visit			4 days prior to HLAB visit			
Take Control		X	X	X	X	X	X	X	
Treatment Referral								X	
Follow-Up Telephone Interview									X
Final Subject Disposition									X
HLAB: Cue Reactivity Paradigm - Week 3 - VAS craving, EM, and SAM				X			X		
TLFB	X	X	X	X**	X	X	X	X	
EtG ^c	X			X			X		
Brief Drinking Questionnaire	AS NEEDED								
Exit Interview								X	
SAM – Post Validation of Pictures							X		
ACQ-SF-R	2X pre/post			2X pre/post			2X pre/post		
PACS		X			X	X	X	X	
Fagerström Test for Nicotine Dependence		X							
Smoking quantity/frequency and nicotine use		X	X	X	X	X	X	X	
PSQI		X						X	
POMS		X			X			X	
Medication Adherence Questionnaire (MAQ)		X							
Self-Report Habit Index (SRHI)		X						X	

**must be abstinent for 3 days prior (based on self-report).

EOS - end of study. These assessments are to be done at Week 8 or if the subject discontinues early and agrees to a final clinic visit.

^a Test for opioids, cocaine, amphetamines, barbiturates, methamphetamine, tetrahydrocannabinol (THC), buprenorphine, methadone or benzodiazepines.

^b Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine, gamma glutamyl transferase (GGT).

^c Sitting blood pressure and heart rate.

^d AEs, concomitant medications, CIWA-AR, and drug compliance reminder.

^e EtG – ethylglucuronide urine alcohol onsite test.

7. Study Interventions

7.1. Investigational Products: Varenicline Tartrate and Placebo

Varenicline tablets in 0.5 mg strength will be over encapsulated and supplied by each site's contracted pharmacy, along with identical matching placebo capsules. Capsules in identical blister packaging configurations will be prepared in kits for each subject containing one blister card with 7 days of drug/placebo for each week of drug/placebo administration + 2 extra blister cards (with enough drug/placebo for one week in the event that a subject loses or misplaces an entire blister card, or is late for an appointment and needs an additional blister card until the next appointment is scheduled).

7.2. Investigational Product Storage

Kits should be stored at room temperature (within the range of 59°F to 86°F) in a secured area at the clinical site.

7.3. Investigational Product Dispensing

One blister card containing 7 days of drug/placebo and 1 additional (emergency) blister card containing 7 days of drug/placebo will be distributed after randomization, Week 1, Day 1. Each week the subject will receive a new blister card with enough medication for 7 days of drug/placebo. The extra blister card will be collected at the end of the study or at the next clinic visit if drug/placebo was used during the week prior. The 2nd emergency blister card will be dispensed if the subject returns the 1st used emergency blister card prior to the end of the study.

7.4. Investigational Product Accountability

The site principal investigator (PI) or designated study personnel will maintain a log of the receipt of all investigational products and record of dispensing of all investigational products to the subject. Investigational product for each subject will be inventoried and accounted for throughout the trial. The site PI or his/her staff will count the capsules remaining at the end of the study and record the capsules count on the appropriate drug accountability form. Subject compliance with investigational product will be assessed by comparing unused capsule count to dispensing logs and dosing records (number of capsules dispensed, number of capsules prescribed, versus the number returned). Subjects will also be asked to account for any missing capsules. If the blister card is not returned, the subject will be asked to report daily drug self-administration.

7.5. Investigational Product Administration

Varenicline will be self-administered by subjects once or twice daily after eating and with a full glass of water beginning on Day 1, Week 1 and continuing through Week 6, day 7. First dose will be taken in the study clinic on the day of randomization. Subjects will be provided with water and a snack to take with first dose. Dose will be titrated, as tolerated, to a target dose of 1 mg twice a day of varenicline. Dose titration, maintenance and taper will occur as shown in [Table 2](#).

Table 2: Schedule of Administration of Investigational Products

Study Period	Time Period	AM Dose (# of capsules)	PM Dose (# of capsules)
Titration	Week 1, Days 1- 3	0.5 mg (1)	None
Titration	Week 1, Days 4-7	0.5 mg (1)	0.5 mg (1)
Maintenance	Weeks 2-6	1.0 mg (2)	1.0 mg (2)

Capsules should be swallowed whole and should not be cut, crushed, or chewed. Capsules should be taken with food and water.

Missed Doses: If a subject misses more than one dose of investigational product, he/she will be instructed to re-start taking the investigational product at the dosage level that s/he was taking before stopping. If one dose of investigational product is missed, he/she should take it immediately unless it is close to the time for the next dose. In that case the subject should skip taking the missed dose of investigational product and wait until the usual time to take their next dose of investigational product. The subject should not double up doses.

Dose Reduction and Discontinuation. For problematic nausea (or other mild-moderate AEs), the dose may be reduced to 1 mg once daily and then 0.5 mg once daily. If the AE resolves at the lower dose, another attempt to increase the dose to the target of 1 mg twice daily is appropriate at the clinical staff designated prescriber's discretion.

7.6. Take Control Behavioral Platform

The behavioral platform “Take Control” (Devine et al., 2016) will consist of a series of 7 computerized modules. Subjects will view a single module of “Take Control” at each clinic visit starting after randomization on Week 1, Day1. If a visit is missed, missed modules will be reviewed at the next visit. The paper versions of the modules are not to be given to the subject to take home and must remain at the clinic. The intervention is derived from a self-help approach developed by NIAAA that provides evidence-based, field tested information for individuals with alcohol problems, and suggestions for making changes in their drinking. The NIAAA material is publically available in a NIAAA booklet entitled “Rethinking Drinking” and on a NIAAA website <http://rethinkingdrinking.niaaa.nih.gov>. Delivering these materials in a computerized method in this trial has the advantage of standardizing the amount of educational material received by the subject.

7.7. Concomitant Medications

Based on varenicline characteristics and clinical experience to date, varenicline has no clinically meaningful pharmacokinetic (PK) drug interactions.

Safety and efficacy of varenicline in combination with other smoking cessation therapies have not been fully evaluated:

- Bupropion: varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.
- Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect

nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. For study inclusion, subjects will be asked to discontinue use of NRT during their participation in the study.

For study inclusion, subjects cannot have taken any anti-convulsants, hypnotics, barbiturates, antipsychotics, psychomotor stimulants (such as methylphenidate), or benzodiazepines within 5 half-lives prior to the date of randomization. In addition, if a subject is taking a medication for depression or anxiety, he or she must have been taking a stable dose in the 2-months prior to randomization and plan to continue during the study. This includes drugs such as the following:

- selective serotonin reuptake inhibitors (SSRIs)
- dual uptake inhibitors
- serotonin-norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- monoamine oxidase inhibitors (MAOIs)

Pharmaceutical treatments approved for treatment of alcoholism or treatments known to be used off-label or experimentally for treatment of alcoholism are prohibited during the study. The following drugs approved for the treatment of alcoholism are also prohibited:

- Oral naltrexone (Revia, Depade)
- Depot naltrexone (Vivitrol)
- Disulfiram (Antabuse)
- Acamprosate (Campral)
- Nalmefene (Selincro)

In addition, a list of prohibited drugs that are prescribed off-label or experimentally for the treatment of alcoholism will be included in the Manual of Procedures and updated during the study if new drugs are identified. Also, if a subject reports using a drug or having been prescribed a drug to treat alcoholism during the trial, they will be asked to discontinue its use.

Subjects will be instructed to check with study staff before taking any new medications or stopping current medications. Subjects will be informed that starting any new medication without consulting study staff could pose health risks and/or result in their discontinuation for the study drug.

Management of investigational products and concomitant medications during the study is at the discretion of the PI or designated medical doctor. The PI or designee may consult with the medical monitor if there are questions.

8. Study Procedures

8.1. Recruitment of Subjects

Subject recruitment methods at each site will be based on their local population; however, standard tactics will be used (i.e., flyers, newspaper advertisements, radio advertisements, and television advertisements). Local institutional review boards (IRBs) and NIAAA will approve all advertising materials used for subject recruitment. Interested candidates responding to recruitment materials by telephone will be asked to complete a standardized telephone interview that includes questions about their drinking behavior, health status, interest in participation, and availability for the entire trial. Study staff will ask these questions without revealing the entry criteria for the study. Candidates who report drinking and other information consistent with the entry criteria and appear to be available and interested in the study will meet with the investigator or designated investigational staff ideally within 14 days after the initial inquiry to start the informed consent and assessment process.

8.2. Informed Consent

At the first screening visit, candidates will meet with either the PI or his/her designee and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the local site's IRB. Subjects must have blood alcohol content (BAC) of 0.000 measured by breathalyzer when signing the informed consent document (tested shortly before or just after providing consent). Repeat measurements of BAC are permitted at the discretion of the investigator. Subjects will be given a copy of the signed informed consent form.

8.3. Selection and Withdrawal of Subjects

8.3.1. Inclusion Criteria

To be eligible, the subject must:

1. Be at least 21 years of age.
2. Meet the DSM 5 criteria for alcohol use disorder of a least moderate severity (AUD-MS).
3. If male, report drinking a weekly average of at least 35 drinks per week or if female report drinking a weekly average of at least 28 drinks per week for the 28-day period prior to consent.
4. Have at least 1 heavy drinking day (4 or more drinks for women/5 or more drinks for men) during the 7-day period prior to randomization.
5. Be seeking treatment for AUD and desire a reduction or cessation of drinking.
6. Be able to verbalize an understanding of the consent form, able to provide written informed consent, verbalize willingness to complete study procedures, able to understand written and oral instructions in English and able to complete the questionnaires required by the protocol.

7. Agree (if the subject is female and of child bearing potential) to use at least one of the following methods of birth control, unless she is surgically sterile, partner is surgically sterile or she is postmenopausal:
 - a. oral contraceptives,
 - b. contraceptive sponge,
 - c. patch,
 - d. double barrier (diaphragm/spermicidal or condom/spermicidal),
 - e. intrauterine contraceptive system,
 - f. levonorgestrel implant,
 - g. medroxyprogesterone acetate contraceptive injection,
 - h. complete abstinence from sexual intercourse, and/or
 - i. hormonal vaginal contraceptive ring.
8. Be able to take oral medication and be willing to adhere to the medication regimen.
9. Complete all assessments required at screening and baseline.
10. Have a place to live in the 2 weeks prior to randomization and not be at risk that s/he will lose his/her housing in the next 2 months.
11. Not anticipate any significant problems with transportation arrangements or available time to travel to the study site over the next 2 months.
12. Not have any unresolved legal problems that could jeopardize continuation or completion of the study.
13. Provide contact information of someone, such as a family member, spouse, or significant other, who may be able to contact the subject in case of a missed clinic appointment.
14. Be willing to discontinue the use of nicotine replacement therapies prior to randomization and refrain from using nicotine replacement therapies during the course of the study.
15. Have a BAC by breathalyzer equal to 0.000 when s/he signed the informed consent document.
16. If taking a medication for depression or anxiety, must have been taking a stable dose in the 2-months prior to randomization and plan to continue during the study. This includes drugs such as the following:
 - a. SSRIs
 - b. dual uptake inhibitors
 - c. SNRIs
 - d. tricyclic antidepressants
 - e. MAOIs
17. Be someone who in the opinion of the investigator would be expected to complete the study protocol.

18. Agree to the schedule of visits, verbally acknowledge that s/he will be able to attend each scheduled visit, participate in phone visits and that s/he does not have any already scheduled events or a job that may substantially interfere with study participation.

8.3.2. Exclusion Criteria

To be eligible, the subject must not:

1. Have current (past 12 months) dependence on any psychoactive substance other than alcohol and nicotine, including sedatives and hypnotics, as defined by DSM-5 criteria.
2. Have a urine toxicology screen positive performed during screening or baseline for any of the following substances:
 - a. benzodiazepines,
 - b. cocaine,
 - c. opioids,
 - d. amphetamines,
 - e. buprenorphine,
 - f. methadone,
 - g. barbiturates,
 - h. oxycodone,
 - i. tetrahydrocannabinol,
 - j. and/or methamphetamines.

Note: Testing for tetrahydrocannabinol (THC) will be included in the urine drug test; however, subjects who test positive for THC are still eligible to participate in the study unless they are dependent on marijuana as indicated by DSM-5 criteria. The results for THC will be recorded for information only. If positive for opioids or oxycodone but recent opiate use for acute pain is reported by the subject, then the subject can be included at the discretion of the investigator.

3. Have Visual Analogue Scale (VAS) craving rating of alcohol cue question (“How strong is your craving to drink alcohol”) < 3 points higher than water cue during the mini cue reactivity session prior to randomization.
4. Have been hospitalized for alcohol intoxication delirium, alcohol withdrawal delirium, alcohol-induced persisting dementia or amnestic disorder, or have had an alcohol withdrawal seizure, alcohol-induced psychotic disorder with a primary diagnosis of AUD or a history of any seizure disorder.
5. Have participated in any behavioral and/or pharmacological intervention research study for the treatment of alcoholism or smoking cessation within 3 years prior to signing the informed consent.
6. Be mandated by the court to obtain treatment for alcohol-dependence, or has probation or parole requirements that might interfere with study participation.

7. Be anyone who in the opinion of the investigator could not be safely withdrawn from alcohol without medical detoxification.
8. Have undergone medical detoxification (e.g., reports using a benzodiazepine) during the screening phase (prior to randomization).
9. Have been treated with a pharmacotherapy for alcohol use disorder within 6 months prior to randomization.
10. Report heavy drinking alcohol within 3 days on TLFB prior to screening and have a negative result on EtG urine test.
11. Have taken any anti-convulsants, hypnotics, barbiturates, antipsychotics, psychomotor stimulants (such as methylphenidate), or benzodiazepines within 5 half-lives prior to the date of randomization.
12. Have taken buprenorphine or methadone in the last 30 days prior to the date of randomization.
13. Have any of the following, based on DSM-5 criteria as assessed using the MINI:
 - a. Current or lifetime diagnosis of psychotic disorders,
 - b. Current bipolar disorder,
 - c. Current major depressive episode,
 - d. Current (past 3 months) eating disorder (anorexia or bulimia), or
 - e. Within past year diagnosis of panic disorder with or without agoraphobia.

Note: Subjects diagnosed with psychiatric disorders not specifically excluded above may be included at the discretion of the PI as long as the concurrent treatment for the comorbid psychiatric condition does not compromise the study integrity by virtue of its type, duration, or intensity.

14. Have any of the following:
 - a. attempted suicide ever,
 - b. current (past year) suicidality risk in accordance with DSM-5 criteria as assessed using the MINI (see note below about assessment of subjects diagnosed at low risk),
 - c. current (since screening MINI) suicidality risk as indicated during the conduct of the C-SSRS with concurrence after a study physician's evaluation if the response to C-SSRS questions 1 or 2 is "yes").

Note: The MINI suicidality module rates scores of 1 to 8 as a diagnosis of low risk of suicidality. As the MINI questions that could result in a low risk score are considered inadequate to fully determine the potential suicidal risk of an individual (e.g., "Feel hopeless" and "Think that you would be better off dead or wish you were dead?" responses of "yes" dictates a score of 1 for each question), any subject who scores in the low risk category should be evaluated further by a study physician who should document whether the subject is appropriate for study inclusion based on his/her clinical judgment of the potential suicide risk of the

subject. Likewise, if the subject responds “yes” to either the first two questions on the screening C-SSRS performed on the day of randomization as a final eligibility check, the subject should also be evaluated by a study physician for current suicidality risk, who should document the subject’s suitability for study inclusion.

15. Have moderate or serious dementia as assessed by clinical exam.
16. Be pregnant or breast-feeding or have plans to become pregnant at any time during the study.
17. Have clinically significant abnormal laboratory values, including elevation of liver enzymes (AST, ALT) 5-fold above the upper limit of normal (ULN), or bilirubin greater than 2 times the upper limit of normal.

Note: If the subject has values of liver enzyme that are 3.0-to-4.9 fold above the ULN and bilirubin that is 1.5-to-1.9 fold above the ULN of normal, these assessments should be repeated and if still in this range or higher, the subject should be referred to their physician for further follow-up.

18. Have abnormal calculated creatinine clearance defined as < 80 mL/min for subjects ≤ 55 years of age and < 65 mL/min for subjects > 55 years of age.
19. Have a serious or unstable medical illness or any potentially life-threatening or progressive medical condition other than addiction that may compromise subject safety or study conduct.
20. Be currently undergoing psychotherapy by a licensed therapist or psychiatrist for alcohol problems.

NOTE: Current psychotherapy should be considered on a case-by-case basis.

Psychotherapy for a disorder that may be related to the subject’s use of alcohol should be exclusionary. However, shorter term focused behavioral therapy for defined problems for non-alcohol related problems may be acceptable.

21. Have data suggesting cirrhosis of the liver (albumin < 3.2 g/dL, or ascites by physical exam).
22. Have been previously treated with varenicline for any reason.
23. Have had gastric bypass surgery.
24. Have a history of atherosclerotic cardiovascular disease including angina pectoris, myocardial infarction, stroke, transient ischemic attack, peripheral vascular disease or revascularization procedures or clinically significant ECG indicative of cardiovascular disease. Note: stable hypertension is not exclusionary.

8.4. Eligibility Screening Assessments

After the subject signs informed consent, screening may begin. After providing written informed consent, subjects complete the Screening Visit for initial evaluation of eligibility. A mini-cue session familiarizes subjects with the human lab setting and identifies non-cue-reactive subjects for study exclusion (VAS craving rating of alcohol cue < 3 points higher than water cue on the item, “How strong is your craving to drink alcohol?”)

During the first screening visit (additional visits are permitted if needed), subjects will undergo the following assessments:

- Alcohol breathalyzer (must have a BAC of 0.000 to continue with assessments)
- Informed Consent
- Demographics and locator form
- Urine drug screen
- Medical history
- MINI Version 7.0
- Clinical chemistry
- Hematology
- Pregnancy test for females of child bearing potential and birth control methods, if female
- Vital signs
- ECG
- EtG
- Mini-Cue Session
- Mood/Behavior/Thinking questions
- TLFB for the previous 28 days
- Prior medication use
- CIWA-AR

Prohibitions and Restrictions:

Potential subjects must be willing/able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Refrain from drinking alcoholic beverages for 3 days prior to the human lab sessions.
- Refrain from consuming caffeine after arriving for the lab session until study assessments are completed.
- Refrain from smoking during the lab session except for designated smoke breaks (approximately 1-1.5 hours prior to lab session).

Subjects will be instructed that if they are taking a medication for depression or anxiety that they should continue to do so throughout the study. They will also be instructed not to take varenicline prescribed from a doctor outside of the study during their time in the study and that they should report any new medications they are taking at each visit or telephone contract.

The above assessments can be performed in any order except that it is recommended to perform physical examinations including vital signs prior to blood draws. If any of these assessments reveal that the subject is not eligible for the study, screening can be immediately terminated.

Clinical chemistry tests may be repeated at the discretion of the investigator if the first assessment yields values outside normal laboratory limits. The eligibility checklist will be reviewed, and if the subject is still eligible after the assessments are completed at the first screening visit (or additional screening visits), the subject will be scheduled for the final eligibility baseline visit. It is recommended that hypertensive subjects be referred to their primary care physician for additional assessment and possible treatment, and then be further evaluated for study inclusion.

Mini Cue Session:

Subjects will be escorted to a comfortable chair in a lighting-controlled, sound-attenuated room for the mini alcohol cue reactivity session. Following a 90 second rest period, a water bottle will be placed on a small table after which subject will be instructed to pick it up and smell it, but not drink it, for a duration of 90 seconds. Immediately after the subject will complete a series of four (4) VAS craving questions and a VAS question ascertaining beverage liking. The water will be removed and after a 90 second rest period, the subject's favorite alcoholic beverage will be placed on a small table after which subject will be instructed to pick it up and smell it, but not drink it, for a duration of 90 seconds. Immediately after the subject will complete the same five (5) VAS craving questions.

8.5. Baseline and Final Eligibility Assessments

If the subject is eligible after performing all the initial screening assessments, s/he will be scheduled to start the study and will come to the clinic for a final eligibility check approximately 1 week after the initial screening visit for following assessments:

- Alcohol breathalyzer (must have a BAC of 0.02 or less to continue with assessments)
- Urine drug screen
- Update medical history
- Physical exam and weight
- Vital signs
- CIWA-AR
- C-SSRS*
- Mood/Behavior/Thinking questions
- Pregnancy test for females of child bearing potential
- Birth control methods, if female
- Prior medications update
- TLFB

*Note that the MINI will be used to rule out subjects who attempted suicide in the past year and current (past year) suicidal ideation at initial screening, with the C-SSRS providing an update on current suicidal ideation since screening.

An eligibility checklist will be completed and reviewed by a study investigator and, if the subject is still eligible, he/she will complete the following questionnaires:

- PACS
- Drinking Goal
- Modified Fagerström Test for Nicotine Dependence
- Smoking Quantity Frequency and Nicotine Use Questionnaire
- PSQI
- POMS
- MAQ
- SRHI

8.6. Measures Taken to Minimize/Avoid Bias

8.6.1. Randomization (Day 1)

If eligible for the study, subjects will be randomized in an approximate 1:1 ratio to receive either varenicline or placebo using a stratified permuted block randomization procedure with any nicotine use versus no use in the past week as the stratification variable.

A computer-generated randomization code will be used to assign subjects to treatment group at each individual site.

If the subject is randomized and is never dispensed study drug, then the subject will be considered a randomization failure and an additional subject will be randomized with the next randomization sequence at the time he/she is randomized at that site. Likewise, if the subject was randomized and then is determined to not be eligible for the study, and never received study drug, then another subject will be randomized such that the total numbers of subjects who were eligible, randomized, and dispensed study drug meet the enrollment goals. In the case of a subject who was eligible, randomized, and dispensed study drug but did not return for follow-up visits, this subject will not be replaced. Any subject who received study drug but was later determined to be ineligible will likewise not be replaced. The reason(s) that a subject was considered a randomization failure or screen failure will be documented in source documents and CRFs.

8.6.2. Blinding

Varenicline and placebo capsules will be identically matched in appearance and the blister cards labeled not to reveal the drug identity. The site investigator or designated approved study physician will make the decision to un-blind the identity of the investigational product in the event that the study blind needs to be broken to make medical decisions regarding subject treatment. If it is determined that unblinding is necessary to assess AEs or SAEs for expedited reporting, NIAAA may decide to request unblinding of a subject. The site investigator will automatically notify the NIAAA that a subject was unblinded who will notify the Medical Monitor.

8.7. Interventions on Week 1, Day 1

Subjects will view a single module of Take Control that is expected to have a run-time of 10-15 minutes during this clinic visit prior to dispensing study drug.

After the subject is randomized, he/she will receive the first blister pack of study drug. Site staff will explain the dosing plan to the subject.

Every study subject will be provided with a wallet card and instructed to carry this card that identifies the potential investigational products that s/he could be taking during the study. The card will provide the name and 24-hour phone number of the investigator (physician) at the site who can be contacted in the event of an emergency. The card will also instruct the non-study physician rendering emergency care to contact the study physician and inform him/her about the care.

If possible, clinic visits should be scheduled on the same day of the week that the subject received the first dose of study drug, but a 3-day window is allowed for conducting visits within the scheduled study week. Visits may be scheduled and conducted on any day of the week. Visits can be conducted outside of the scheduled study week, but only based upon subject request (e.g., for reasons related to patient non-compliance with the study schedule). Each subject will receive a visit schedule to take home for future reference.

8.8. Weeks 1 Telephone Contact

On Week 1, Day 3 subjects will be called for a safety assessment and given a reminder to begin taking 0.5 mg, BID the next day, Week 1, Day 4. A second reminder call will be made on Week 1, Day 7 to remind the subject to escalate dose to 1 mg, BID the next day, Week 2, Day 1. The same assessment will be performed on during Week 1 phone contacts as all other telephone contacts (see section [8.10](#)).

8.9. Maintenance Phase

During Study Weeks 2 through 6 of the maintenance phase of the study, subjects will be seen in person at the clinical site 5 times.

An alcohol breathalyzer will be administered at each visit, prior to any study assessments, to determine if the subject meets the BAC requirement of a $BAC \leq 0.020$ before proceeding with assessments. A urine drug test will be performed at each visit. At each of the clinic visits, subjects will meet with one or more study staff members who will systematically assess AEs since the last visit, take vital signs, administer questionnaires (CIWA-AR and C-SSRS), inquire about other medication use and assess drinking by TLFB. Pregnancy test for women of child-bearing potential and birth control methods (if female) will be collected in accordance with the schedule in [Table 1](#). In addition, subjects will complete the battery of questionnaires in accordance with the schedule in [Table 1](#).

A reminder telephone assessment will occur 4 days prior to the Week 3 and the Week 6 visit. During the telephone contact the subject will be reminded of the requirement of 3 days abstinence before the HLAB visit. The final in-clinic assessment will occur during Week 7. This visit should occur after the subject takes the last dose of study drug.

Subjects will view a single module of Take Control that is expected to have a run-time of 10-15 minutes during each clinic visit. After completion of the Take Control module, a new supply of investigational product will be given and the blister cards from the previous period will be collected and a capsule count will be performed for accountability. Blister cards with unused capsules will be returned to the subject. The dosing schedule will be reviewed. The subject will be instructed to bring the blister cards with them to the next visit so the site staff can perform drug accountability (capsule counts). The subject will also be instructed to contact site staff if they are experiencing any intolerable AEs and are contemplating drug discontinuation.

Additional in-clinic visits are permitted under the protocol, if needed, due to the following circumstances: (1) the subject has concerns either about the medication or their drinking and wishes to be seen at a time other than their next scheduled in-clinic visit, or, (2) the subject has missed a visit and wishes to resume regular participation before their next scheduled visit, (3) the subject has reported some change in health, functioning, or circumstances which necessitate a visit to conduct safety assessments and evaluate the risk of continued participation in the trial, or (4) clinical laboratory measurements need to be repeated.

Subjects desiring additional counseling or professional therapy for non-crisis psychiatric matters (e.g., marital problems, work issues) should be encouraged to postpone such activity until their study participation is concluded.

8.10. Telephone Assessments

The brief telephone interview (approximately 10 minutes) will occur in accordance with the schedule in [Table 1](#). or if a subject misses a clinic visit but agrees to check-in by telephone to assess AEs, concomitant medication use and the emergence of withdrawal symptoms, to encourage the subject to continue taking investigational products, to verify that the subject is taking the prescribed dose, and to remind the subject of the next scheduled visit and dose increases. A summary of the telephone script follows:

1. AEs: An open-ended question will be asked as follows: “How have you been feeling since your last clinic visit or phone contact?” If the subject reports a new AE, the resolution of an AE, or a change in the severity of an AE, ask additional questions to determine the severity and dates of occurrence or resolution.
2. CIWA-AR: Subjects will be assessed for the emergence of withdrawal symptoms using the CIWA-AR. The subject may be asked about changes in drinking status after responses to the CIWA-AR interview indicate significant withdrawal.
3. Concomitant Medications: Ask the following question: “Have you taken any new medications since you were last seen in the clinic or since our last call? If the subject responds affirmatively, record the name of the medication, the daily dose, route of administration, and reason used. If the medication is contraindicated for the study, then notify a study physician, nurse practitioner, or physician assistant for follow-up with the subject.
4. Drug Compliance: Verification that the subject is taking the prescribed dose and a reminder to take investigational product and to return the blister card(s) with untaken capsules at the next visit will be made. During the Week 1 telephone contacts (Day 3 and Day 7), the subject will be reminded of the drug escalation schedule.

5. Reminders: Remind the subject of their next scheduled clinic visit, and adjust the date within the visit week if they have a conflict. During the Week 2 and Week 5 call the subject will be reminded of the 3 days abstinence requirement prior to the HLAB visit.

8.11. HLAB Paradigm Testing

Subjects must fulfill the following criteria before conducting the HLAB session:

Subjects must fulfill the following criteria before conducting the HLAB session:

1. Must have taken at least 0.5mg per day during the 3 days prior to the HLAB session.
2. Must have BAC = 0.00 prior to starting the HLAB session.
3. Must have 3-days of self-reported abstinence prior to the HLAB day (TLFB).
4. Must have CIWA score < 8.

If any of the above conditions are not met, then the lab session cannot be conducted at that visit. If the subject failed for any of the reasons above, they can be rescheduled for another lab session visit in order meet the required conditions, and only if lab session occurs no more than 7 days thereafter. If a subject fails any of the required criteria on the rescheduled visit, then the subject is excluded from the entire study. On Week 3, Day 1 and Week 6, Day 1 subjects will be seen in-person in the clinic for assessments and questionnaires in accordance with [Table 1](#) and the human lab paradigm testing will be conducted. The human lab session will last for approximately 2.5 hours (see [Table 3](#) for summary). Approximately, 1-1.5 hours prior to the lab session, allow subject who smoke to have an opportunity to smoke. All subjects will be asked (but not required) to drink 4oz of water; and a restroom break prior to the lab session will be provided.

Laboratory sessions should occur in the late afternoon if possible. Upon confirmation of eligibility for the conduct of the HLAB test and completion of clinical assessments, subjects will be escorted to a comfortable chair in a lighting-controlled, sound-attenuated room for alcohol exposure. A 3 affective image (positive, neutral, negative affect) X 2 beverage (alcohol, water) within-subjects, block factorial design (6 repeated measures) will be employed for the cue reactivity manipulation. All six mood-beverage combinations will be presented to each subject.

For each of the six cue combinations, a computer screen displays the appropriate emotion-evoking affective images, followed immediately by exposure of the subject's favorite alcoholic beverage or water such that the subject will see, touch, and smell the beverage, but not drink. The affective picture viewing procedure consists of pictures on a large screen directly in front of the participant, and includes positive (e.g. adventure sports, intimate kissing), negative (e.g., traumatic physical injuries, dangerous weapons) or neutral (e.g. household objects, mushrooms) images. For each trial, participants will be exposed to a set of 12 pictures within the relevant affective condition. Subjects will be instructed to look at each picture for the entire presentation time and remember the mood evoked by the pictures. Immediately following the picture sequence, the computer display goes blank, and subjects are then presented with either their preferred alcoholic beverage (e.g. vodka, lager beer) or bottled water. The alcohol or water beverage is presented in the subject's preferred mode of consumption (e.g., small tumbler for vodka, Pilsner glass for beer), and subject is instructed to hold and smell the beverage for 90 seconds. Specific alcohol brand preferences are accommodated whenever possible, including

choices of mixers (e.g., vodka will be poured into a glass along with orange juice if the favorite drink were a screwdriver).

Subjects will be instructed to “focus on the sensation you have while smelling the alcohol or water beverage and continue to feel the mood stirred up in your imagination by the pictures you have just viewed.” The beverage cue exposure period will last for 90-seconds. Following the beverage exposure period, the beverage will be removed. Subjects then will complete all subjective craving and other ratings by making selections from the computer screen. The procedure will be repeated for the remaining mood-beverage combinations.

Order of affect-beverage combinations will be determined by computer-generated randomization code to control for potential order effects – see HLAB Testing Day protocol. Data will be collected in response to each affect-beverage pair. Upon completion of all six reactivity trials, subjects will view each picture again and record a SAM rating, relax, are debriefed, and complete measures of craving and mood to verify a return to baseline.

Table 3: Events for HLAB

HLAB Start	Subject arrives; all assessments for Study Week #3 or Week #6 are conducted (except Take Control and blood draw for clinical chemistry)
HLAB Prep	Subject prepped for cue session (subject provided with instructions and practice trial conducted)
HLAB Trials	<p>Step 1 – Mood induction: subject exposed to block of 12 affective images (pleasant, unpleasant or neutral).</p> <p>Step 2 – <i>In vivo</i> beverage cue: alcohol or water in front of subject for 90 seconds while recalling picture-induced mood</p> <p>Step 3 – Ratings: subjects complete VAS craving, SAM and manipulation check in presence of beverage cue</p> <p>Step 4 – Beverage removed from testing area after completion of ratings</p> <ul style="list-style-type: none"> • Repeat steps 1-4 for remaining affect-beverage trial combinations (six trials total) • All pictures viewed again and SAM rating recorded for each. • restroom break
HLAB Post	Debriefing and relaxation period, ACQ-SF-R to verify that craving has returned to baseline. Take Control will be viewed prior to the end of the clinic. Blood will be drawn for clinical chemistry.

8.12. Final Clinic Visit

The final clinic visit occurs during Week 7; at which time the subject has completed taking investigational product. The subject will complete study assessments in accordance with [Table 1](#) and will be provided with a referral to a treatment program for their AUD. If a subject withdraws from the study early for any reason, the subject should be asked to return to the clinic for the conduct of the final clinic visit assessments.

8.13. Telephone Follow-up

Subjects will be contacted by telephone for a follow-up interview 2 weeks after the final in-clinic visit. During the telephone follow-up interview, the subject will be asked about any ongoing AEs that they may have been experiencing at the last clinic visit and any newly emerged medical conditions/AEs since that visit. To prompt reporting of new AEs, the subject will also be asked about any ongoing or new medication use.

8.14. Duration of Subject Participation

The total time period that each individual subject will participate is up to 10 weeks including up to 2 weeks for screening, 6 weeks of study interventions one end-of-study visit, and a final safety follow-up telephone contact from 2 weeks after completion of study drug dosing.

8.15. Dose-adjustment Criteria

8.15.1. Safety Criteria for Dose Adjustment or Stopping Doses

The PI or sub-investigator will follow the protocol to identify and intervene with subjects experiencing clinical deterioration during study participation. Criteria to determine when a subject requires a higher level of care and discontinuation from the trial intervention are detailed below.

8.15.1.1. Investigational Product Dose Reduction

The daily dosage of investigational product may be reduced by the study physician for any AE determined, by the study physician, to compromise the subject's ability to maintain activities of daily living or if the subject reports undue discomfort. The dose may be reduced to 1 mg once daily or 0.5 mg once daily. If the AE resolves at the lower dose, another attempt to increase the dose to the target of 1 mg twice daily is appropriate at the physician's, nurse practitioner's, or physician assistant's discretion. However, it should be noted that dose reductions to less than 0.5 mg daily during Week 2 will make the subject ineligible for the study and they will be withdrawn from the study.

8.15.1.2. Investigational Product Discontinuation

Subjects who are discontinued from investigational product after the Week 3 assessments should continue in the study and complete all assessments. If the subject discontinues before this time point, then they will not be eligible for the Week 3 HLAB assessment and will be discontinued from further study participation.

- a. **Pregnancy.** Females who become pregnant during the course of the study interventions will be immediately discontinued from the investigational product. The

investigator must report a pregnancy within 1 working day of the site being aware to the NIAAA Study Manager and the Medical Monitor.

- b. **Physical Illness.** Subjects will need to be removed from investigational products if they have a serious illness or a disabling condition that precludes them from taking the investigational product.
- c. **Elevated Liver Enzymes.** Subjects whose ALT or AST is greater than 5X ULN should have these tests repeated as soon as possible and if still elevated should discontinue investigational products. If the repeat values are less than the criteria above, the subject should be monitored using clinical judgment. If ALT or AST levels are in the range of 3-4.9x ULN and total bilirubin is in the range of 1.5x-1.9x ULN, then the subject may be at risk for clinically significant hepatic dysfunction. The first action will be to have the laboratory test repeated as soon as possible to confirm the result. If the value was confirmed, then the subject will be withdrawn from receiving the study drug but will continue to be followed for the duration of the study as long as the subject agrees to continue in the study. Subjects discontinued from investigational products for elevated liver enzymes should be referred to their own physician for follow-up.
- d. Abnormal calculated **creatinine clearance** defined as < 50 mL/min.
- e. **Adverse Events.** If the subject experiences any AEs that are considered study drug related and for which the investigator has determined that continuation of the study drug could be detrimental to the health of the subject, then drug will be reduced for 1 week, then discontinued, or immediately discontinued as described above.

8.16. Subject Withdrawal or Discontinuation Procedures

Each subject has the right to withdraw consent and withdraw from the study at any time. In addition, the investigator may find it necessary to discontinue a subject for any reason, including the occurrence of an AE or noncompliance with the protocol.

In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded and a pregnancy test (females only), vital signs, clinical chemistry, C-SSRS, TLFB and an assessment of AEs will be performed as soon as possible after discontinuation from the study. Other assessments scheduled for the end of study visit will be collected if possible (**Table 1**).

8.17. Situations Requiring Discontinuation from the Study as well as from Investigational Product

It is possible that there will be some subjects who cannot be safely managed in the clinical study even though investigational products have been discontinued. Examples are given below.

- 1. **Increased Drinking.** Subjects whose alcohol problem worsens, and, in the opinion of the site medical staff, require a more intense level of care than provided in the study may have investigational product suspended, and referred to more appropriate care.

2. **Psychiatric Crises.** Examples of psychiatric crises include but are not limited to the following:

- a. Acute psychosis (hallucinations, impaired reality testing, paranoid ideation, etc.) requiring medication and/or hospitalization or intensive outpatient intervention;
- b. Suicidal or homicidal ideation that results in a credible threat of violence directed at oneself or others;
- c. Hospitalization for psychiatric symptoms

Subjects requiring more intensive treatment resulting from acute psychosis or suicidal/homicidal behavior will be referred to local treatment centers, emergency departments, or hospitalization as appropriate, but will not be provided with medication or psychotherapy by study staff.

3. **Absence from the Protocol due to Confinement in a Controlled Environment.** If a subject is confined to a controlled environment (such a hospital or jail where access to alcohol is presumably restricted) for less than 2 weeks, they can resume full participation in the trial if in the judgment of the investigator, the subject is still a good candidate for the study and continues to meet eligibility requirements. Before resuming investigational products the subject should be assessed by the study physician for appropriateness to resume the trial (e.g. any new medications or symptoms, pregnancy test, etc.). The decision to restart study drug at the full dose or titrate to the full dose will be made in the judgment of the investigator based on the subject's time off study drug and past experience with side effects with the study drug.

If a subject is in a controlled environment (such a hospital or jail where access to alcohol is presumably restricted) for 2 weeks or more, the subject will be discontinued from the study.

8.18. Study Termination Criteria

NIAAA may terminate this study prematurely, either in its entirety or at any sites, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to NIAAA in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If NIAAA terminates the study for safety reasons, NIAAA will immediately notify the investigators by telephone and subsequently provide written instructions for study termination.

9. Study Endpoints

9.1. Efficacy Endpoints

9.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is difference between the varenicline and placebo groups on the alcohol craving VAS summary score (and subscale scores) in response to the alcohol cue reactivity human laboratory paradigm.

Confirmatory endpoints for the human laboratory paradigm session include VAS items assessing beverage preference and emotional responsivity to the pictures.

9.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analyzed over the last 4 weeks of the maintenance phase of treatment.

1. Percentage of subjects with no heavy drinking days. A “heavy drinking day” is 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men.
2. Percentage of subjects abstinent from alcohol
3. Percentage of subjects with at least a WHO 2-level decrease in alcohol consumption
4. Percentage of subjects with at least a WHO 1-level decrease in alcohol consumption
5. Percentage of days abstinent per week
6. Percentage of heavy drinking days per week
7. Percentage of very heavy drinking days per week. A “very heavy drinking day” is 8 or more drinks per drinking day for women and 10 or more drinks per drinking day for men.
8. Weekly mean number of drinks per week
9. Weekly mean drinks per drinking day
10. Cigarettes smoked per week among smokers
11. Percentage of subjects with no nicotine use among nicotine users
12. Alcohol craving score (PACS)
13. Sleep quality (PSQI) score
14. Profile of Mood States (POMS) score

9.2. Safety Endpoints

Safety endpoints will be analyzed over the entire treatment and follow-up period.

1. Vital signs
2. Blood chemistries
3. BAC by breathalyzer
4. Urine drug tests

5. AEs
6. ECG results
7. CIWA-AR scores
8. Frequency of subjects with suicidal ideation at any time during the treatment period (C-SSRS)
9. Neuropsychiatric safety variables: Mood changes, Behavior/Thinking changes, increased intoxicating effect of alcohol
10. Concomitant medication use
11. ACQ-SF-R

9.3. Compliance

Compliance will be assessed by self-report of compliance with investigational products and varenicline plasma levels. Compliance will be calculated as the percentage of investigational products taken as prescribed and by the total amount of medication consumed. Participation will be evaluated as the percentage of subjects with complete drinking data.

10. Safety Monitoring Plan

Safety monitoring will be conducted throughout the study; therefore safety concerns will be identified by continuous review of the data by the PI, clinic staff, clinical monitor, medical monitor, and NIAAA.

The IRB, Medical Monitor, PI, Clinical Monitors and NIAAA (or its affiliates) will review any safety concerns throughout the trial. In addition, a data and safety monitoring board (DSMB) will participate in this study. The roles of these individuals/committee are described below.

Medical Monitor: A Medical Monitor has been appointed by NIAAA for the study. The Medical Monitor will be available for making recommendations to the investigator and NIAAA on the severity of any SAEs, and the relatedness to the study interventions. The Medical Monitor will also be responsible for tracking and assessing trends in the AEs reported.

Clinical Monitors: All investigators will allow representatives of NIAAA to periodically monitor, at mutually convenient times during and after the study, all study data. These monitoring visits provide NIAAA with the opportunity to evaluate the progress of the study and to obtain information about potential problems. The monitors will assure that submitted data are accurate and in agreement with any paper source documentation used; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by NIAAA's representatives will be scheduled at appropriate intervals but more frequently at the beginning of the study. A monitoring visit soon after the first two subjects have been randomized is planned. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines, monitor CRFs against source documents, review AEs and SAEs, and perform drug accountability. At the end of the study, they will confirm that the site has the appropriate essential documents on file, advise on storage of study records, and inspect the return and destruction records for unused investigational products.

DSMB: An independent DSMB of external advisors will meet prior to the start of the study, and every 6 months during enrollment and follow-up and at trial end to review safety data. The Board will be blinded to subjects' actual randomized group assignments but may request at any time that the blind be broken by the data center, if concerns arise from the blinded data. Ad hoc meetings will be convened if SAEs occur that are considered at least possibly related to the investigational product.

11. Assessment Methods

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments ([Table 1](#)); the following sections outline the details and procedures associated with

the assessments. All assessments will be recorded on a source document with the exception of staff or subject completed questionnaires.

11.1. Alcohol Breathalyzer

An alcohol breathalyzer will be administered at consent, at screening, and at every in-clinic visit as a safety measure. Acceptable BAC level at consent and HLAB (Week 3, the day of HLAB testing) is equal to 0.000 and less than or equal to 0.020 for all other in-clinic visits prior to performing other assessments.

11.2. Adverse Events and Serious Adverse Events

The investigator and study site staff are responsible for the detection, documentation, classification, reporting, and follow up of events meeting the definition of an AE or SAE.

11.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in severity or frequency.

11.2.2. Serious Adverse Events and Serious Unexpected Adverse Events Definition

An SAE is any untoward medical occurrence that meets one of the following:

- Results in death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information included in the Product Label for the drug.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

11.2.3. Methods/Timing for Assessing, Recording, and Analyzing Safety Endpoints

AEs will be assessed at study visits starting after the first administration of investigational product until the final follow-up visit. However, SAEs will be collected from the time of informed consent onward. General symptoms will be collected via an open ended question: “How have you been feeling since your last visit or the last time we spoke?”

AEs will be documented in the source records, and recorded on the CRFs using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is known, the AE term recorded on the CRF will be the diagnosis rather than a constellation of symptoms. The investigator will assess all AEs for seriousness, relationship to investigational product, and severity. When an event has not resolved by study closure, it will be documented on the AE CRF as “ongoing”.

If a woman has a positive or borderline pregnancy test after enrollment, the NIAAA Medical Monitor will be contacted and the pregnancy will be recorded as an AE. The site will contact the subject at least monthly and document the subject’s status until the pregnancy has been terminated or completed. The outcome of the pregnancy will be reported to the NIAAA Medical Monitor without delay within 24 hours of knowledge of the event if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study physicians until satisfactory resolution (the event either resolved or stabilized and is not expected to resolve in the near term). AEs must be reported up to 2 weeks following completion of, or termination from investigational product administration. At the follow-up telephone contact, AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

11.2.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal clinical laboratory findings (e.g., clinical chemistry) or other abnormal assessments (e.g., from vital signs or ECG), judged as clinically significant by the investigator will be recorded as AEs or SAEs, if they meet the definitions provided in Section 11.2.2. Abnormal laboratory or other findings present at baseline that significantly worsen following start of the study will be reported as AEs or SAEs. Abnormal findings present at the start of the study that do not worsen will not be reported as AEs or SAEs, unless the investigator or designee judges them as more severe than expected for the subject’s condition.

11.2.5. Classification of Adverse Event Intensity and Relationship to Investigational Product

For each recorded AE or SAE, a physician- investigator must make an assessment of severity. For those AEs included in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.03), these severity criteria will apply. For those not listed in the CTCAE, the following criteria will be used:

- | | |
|------------------|---|
| Mild: | An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject’s daily activities. |
| Moderate: | An event that interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. The event is usually ameliorated with additional specific therapeutic intervention. |
| Severe: | An event that interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the |

subject and hospitalization may be required, and typically requires intensive therapeutic intervention.

Life-threatening An event that puts the subject into imminent risk of death without intervention.

In particular, clinical chemistry severity and blood pressure increases will be graded in accordance with the CTCAE version 4.03.

The investigator must make an assessment of relationship to the investigational product based on the following criteria:

- Unrelated:** The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.
- Unlikely:** There is evidence of exposure to the investigational product but there is another more likely cause of the AE/SAE.
- Possible:** There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.
- Probable:** There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.
- Definite** There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

11.2.6. Outcomes and Actions Taken

All unresolved AEs will be followed for a minimum of 14 days (unless the AE is an ongoing pregnancy which must be followed to conclusion) after the subject's final study visit, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized prior to the 14-day period, or the subject is lost to follow-up.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the follow-up period.

For each recorded AE or SAE, the investigator must make an assessment of outcome at the time of last observation, as follows:

- Fatal: The subject died.
- Resolved without Sequelae: The AE or SAE has ended.

Resolved with Sequelae:	The AE or SAE has ended but changes are noted from baseline.
Unresolved – Ongoing:	The AE has not ended and is ongoing at the end of the reporting period (i.e., 14 days after the final Follow-up visit) and the investigator deems that further follow up is not medically required
Unknown – Lost to Follow-up:	Lost to follow-up after repeated unsuccessful attempts to contact the subject.

Actions taken with respect to investigational agents (discontinuation or not) will also be recorded. In addition, if the AE was treated (medications or other physical measures), this will also be recorded.

11.2.7. Reporting Serious Adverse Events

11.2.7.1. 24 hour Reporting Requirements (Initial Report)

Any SAE, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the investigational product, must be reported ***within 24 hours*** of knowledge of the event to the NIAAA Medical Monitor or alternate. Ms. Megan Ryan will coordinate communications to the Medical Monitors. Contact her as follows:

Megan Ryan: (301) 443-4225 (office)

The following information must be provided with the initial report of an SAE or unexpected AE:

- Name of person reporting the SAE/unexpected AE
- Subject's I.D. number
- Name of the PI and institution
- Date the subject signed informed consent
- Date first dose of investigational product was ingested
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of investigational product prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to investigational product (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the investigational product, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-Day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIAAA Medical Monitor/Alternate within 3 days of reporting the event. Required documents that must be submitted include the following:

- SAE Form
- Concomitant Medication CRF pages
- AE CRF pages
- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the investigator's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

These documents must be submitted by either email attachments or via overnight courier.

11.2.7.2. Reporting to the IRB

Unanticipated problems involving risk to subjects or others, SAEs related to participation in the study and all subject deaths should be promptly reported by phone, email, or fax to the local IRB.

Investigators are required to forward safety information provided by the sponsor's representative to the IRB.

11.3. Alcohol Craving Scale – Short Form – Revised (ACQ-SF-R)

The ACQ-SF-R contains 12-items adapted from the 47-item ACQ-NOW developed by [Singleton et al \(1994\)](#) to assess craving for alcohol among alcohol users in the current context (right now). There are 4 subscale scores for compulsivity, expectancy, purposefulness and emotionality and a total score. Each item has a 1 to 7 raw score (from strongly disagree to strongly agree). The sum of the raw scores for each factor is divided by 3 to yield a factor based score. Items 3, 8, and 11 are reverse keyed. A general craving index is derived by summing all items and dividing by 12. This form takes ~5 minutes to complete. This questionnaire will be completed by the subject and will be both the source and CRF.

11.4. Alcohol Cue Human Laboratory (HLAB testing)

Subjective Measures

Alcohol craving in response to each affect-beverage condition is assessed using four individual Visual Analog Scale items (VAS; endpoints marked with a 0 on the left indicating no craving, and a 20 on the right indicating severe craving) adapted from the ACQ ([Singleton et al \(1994\)](#)). The items represent expectancy for positive reinforcement ("Having a drink would make things just perfect"), strength of craving ("How strong is your craving to drink alcohol"), intent ("If I could drink alcohol now, I would drink it"), and lack of control ("It would be hard to turn down a drink right now"). These items will be assessed after each 12-picture block during the Screening,

Week 3 and Week 6 visits to assess the degree of craving elicited during the cue reactivity paradigm.

Emotional reactivity will be assessed using the **Self-Assessment Manikin** (SAM; Bradley and Lang, 1994). The SAM is a 9-point likert/cartoon figure used to assess three dimensions of affect: 1) valence (how happy or unhappy one is) and 2) arousal (calm or excited). Subjects will be instructed to indicate, “How you are feeling right now.” Anchors for the valence dimension include: “unhappy” versus “happy.” Arousal anchors include: “calm” versus “excited.”

The two SAM items will be assessed after each 12-picture block during the Weeks 3 and 6 visits to assess whether the intended emotional reactivity was achieved with during each picture block. Following the Week 6 visit, the two SAM items will be presented after each picture to assess the degree of emotional reactivity on an individual picture level.

The Emotional Behavioral Check questions are two 20-point VAS items to assess 1) “How much did you like the beverage just given to you?” and 2) “Watching the pictures made me feel a STRONG emotion” (with a 0 on the left indicating “None” and a 20 on the right indicating “extremely strong”). The first item will be assessed after each 12-picture block during the Screening, Week 3 and Week 6 visits. The second item will be assessed during visits at which pictures are shown (Weeks 3 and 6). Collectively, these items further assess whether the intended craving and emotional reactivity was achieved with during each picture block.

All subjective measures will be recorded on a CRF. The SAM post validation assessment will be recorded on both source and CRF.

Affective Stimuli

Positive, neutral, and negative pictures are selected from the International Affective Picture System (IAPS) ([CSEA, 1994](#)). Two sets of 12 equivalent images are selected for each affective category (positive, negative, neutral), in order to reduce habituation across the 2 beverage conditions (alcohol and water). Thus, 24 pictures from each affective category will be used. Prior work has verified that the selected affective slides are associated with the expected affective category ([Mason et al-2008](#)).

11.5. Brief Drinking Questionnaire

If a subject has completed the human lab assessment and is withdrawn from the study early and is no longer participating in clinic visits or providing TLFB drinking data but is willing to be contacted by phone at the week most proximal to dropout, then they will be asked a series of six questions that assess quantity and frequency of drinking, heavy drinking, and maximal drinking since the last day that non-missing TLFB data was provided. Phone calls will continue until the end of the treatment period, as deemed acceptable by the patient, to obtain data on the secondary drinking endpoints. The rules regarding standard drinking units (SDU) applies. These data will be recorded on a source document and CRF. This does not apply to subjects who are willing to supply daily drinking data by the TLFB method.

11.6. Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-AR)

The CIWA-AR modified telephone version is an adaptation for telephone administration of the CIWA-AR a brief 10-item measure used to provide a quantitative index of the severity of the alcohol withdrawal syndrome ([Sullivan et al-1989](#)). The CIWA-AR has been used both in clinical and research applications and has demonstrated both reliability and validity ([Sellers et al-1992](#), [Stuppaeck et al-1994](#)). This questionnaire will be administered by a clinical staff member and subject responses will be recorded and will be both the source and CRF.

11.7. Clinical Chemistry

Clinical laboratory tests will be performed at the clinical site's local clinical laboratory. Laboratories performing these assessments should be directly regulated by the College of American Pathologists (CAP) or Clinical Laboratory Improvement Act (CLIA) guidelines. The laboratory will need to provide a copy of current certification. All clinical laboratory data will be reviewed by the investigator for clinical significance. The total blood volume is approximately 72 mL. Additional laboratory samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Clinical chemistry tests include: creatinine, total bilirubin, ALT, AST, and GGT.

Serum creatinine levels will be used to calculate creatinine clearance (CrCl) according to the [Cockcroft-Gault \(1976\)](#) formula as follows:

$$\text{Males} \quad \text{CrCl (mL/min)} = \frac{(140 - \text{age in years}) \times \text{body weight in kg}}{72 \times \text{serum creatinine mg/dL}}$$

$$\text{Females} \quad \text{CrCl (mL/min)} = \frac{0.85 \times (140 - \text{age in years}) \times \text{body weight in kg}}{72 \times \text{serum creatinine mg/dL}}$$

For any laboratory test value outside the reference range that the investigator considers clinically significant:

- The investigator will repeat the test to verify the out-of-range value
- The investigator will follow the out-of-range value to a satisfactory clinical resolution
- A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an AE

11.8. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a 4-page form asking questions about suicidal ideation, intensity of ideation, and suicidal behavior developed by Posner and collaborators at the New York State Psychiatric Institute ([Oquendo et al-2003](#)). This scale is intended for use by trained administrators. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment. Training is required before administering the C-SSRS through a 30-minute interactive slide presentation followed by a question-answer session through the Columbia University Medical Center. Those completing the training are certified to administer the C-SSRS, and will receive a training certificate. As the MINI will be used to establish subject initial eligibility with respect to suicidality, the "Since Last Visit" version of the C-SSRS will be used at each clinic visit starting with Visit 1 at Week 1. At Visit 1,

Week 1, this scale will be used to assess current suicidal ideation since the MINI interview. This questionnaire will be administered by a clinical staff member and subject responses will be recorded on a CRF and will be both the source and CRF.

11.9. Cigarette Smoking Quantity-Frequency and Nicotine Use Questionnaire

A quantity frequency interview at baseline will include three questions to assess cigarette smoking behavior and other tobacco/nicotine containing products use during the study: 1) “Over the past week, on how many days did you smoke cigarettes?”, 2) “On the days you smoked during the past week, how many cigarettes did you smoke on average?”, and 3) “Have you used any other tobacco or nicotine containing products besides cigarettes in the past week (e.g., cigars, cigarettos, pipes, bidis, or smokeless tobacco such as pan, chewing tobacco, or snuff, or nicotine replacement therapies such as patch or gum)?”. At each subsequent visit, the subject will be asked to provide the average number of cigarettes smoked per week since the last visit and about any nicotine use since the last visit. These questionnaires will be completed by the subject and will be both the source and CRF.

11.10. Demographics

Demographics data include the subject’s age, gender, race/ethnicity, marital status, education, employment pattern, occupation, and income level. These data will be collected by site staff on a source document and onto a CRF.

11.11. Drinking Goal

A subject’s drinking goal will be assessed with a single question to determine the desire to completely abstain from drinking alcohol or reduce drinking without abstinence. The data will be completed by the subject on a CRF.

11.12. ECG

A 12-lead resting ECG will be obtained. Any abnormalities will be noted and an assessment of clinical significance will be done by a study physician.

11.13. Ethylglucuronide (EtG)

The ethanol metabolite, ethylglucuronide (EtG) will be assayed in urine samples collected at screening, Week 3 and Week 6 in-clinic visit. Week 3 and Week 6 samples will be stored and frozen for future testing. EtG is a biomarker of recent alcohol consumption that provides an objective measure of abstinence ([Jatlow et al-2014](#)).

11.14. Eligibility Checklist

The Eligibility Checklist which includes all inclusion and exclusion criteria will be reviewed in stages as follows: 1) after screening measures are completed and before scheduling the Study Day 1 visit and 2) prior to randomization on Study Day 1.

11.15. Exit Interview

At the Week 8 visit, the subject will be queried for his/her impression of whether he/she was receiving varenicline or placebo, a question about desire to please people, and about outside drinking support services used during the study. This CRF will be used as the source document.

11.16. Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence will be used to assess smoking status and motivation to change smoking behavior at baseline ([Heatherton et al-1991](#)). This questionnaire will be completed by the subject and will be both the source and CRF.

11.17. Hematology

Hematologic assessment at screening includes: hemoglobin, white blood cells count, absolute neutrophil count, absolute lymphocyte count, and platelets count.

11.18. Locator Form

After signing informed consent, subjects will be asked to provide names, addresses, and phone numbers of several friends and/or family members who can be contacted if the subject cannot be located (Locator Form). This locator form will be used to assist in contacting subjects between visits and at follow-up. This form asks subjects his/her name, address, and phone number and to provide names, addresses, and phone numbers of several friends and family members who can be contacted if the subject cannot be located. This information is essential and will be collected during screening, and will be updated throughout the study as necessary. This information will remain exclusively at the site.

11.19. Medical History

A medical history will be taken for all potential study subjects to assure medical fitness during screening. The medical history will be updated on the day planned for randomization by asking the subject if anything has changed since the initial screening interview.

11.20. Medication Adherence Questionnaire

The Medication Adherence Questionnaire (MAQ) is a 4-item measure of self-reported adherence. Since intentional nonadherence has been shown to be highly predictive of nonadherence during treatment and outcome (Toll et al., 2007 <http://www.ncbi.nlm.nih.gov/pubmed/17454716>), the MAQ may be used as a co-variate. The assessment will be completed by the subject and used as source and CRF.

11.21. Mini Cue Reactivity Session

Subjects will be familiarized with laboratory procedures during a practice neutral-water cue reactivity session during screening. The methodology is presented in [Mason et al \(2009\)](#). Alcohol craving in response to a water and favorite alcohol beverage cue is assessed using four individual Visual Analog Scale items (VAS; endpoints marked with a 0 on the left indicating no craving, and a 20 on the right indicating severe craving) adapted from the ACQ ([Singleton et al](#)

(1994)). The items represent expectancy for positive reinforcement (“Having a drink would make things just perfect”), strength of craving (“How strong is your craving to drink alcohol”), intent (“If I could drink alcohol now, I would drink it”), and lack of control (“It would be hard to turn down a drink right now”). Subject must have a VAS craving rating on the VAS item, “How strong is your craving to drink alcohol?” of alcohol cue ≥ 3 points higher than water cue during this Mini Cue session at screening to be eligible for the study.

11.22. MINI

The MINI (paper version 7.0) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-5 and ICD-10 psychiatric disorders (Sheehan et al-1998). With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies and to be used as a first step in outcome tracking in non-research clinical settings. Diagnoses recorded on the MINI will be recorded on the interview form and entered onto a CRF. The individual items of the Alcohol Use Disorder Module will be also collected on a CRF in addition to all other diagnoses.

11.23. Penn Alcohol Craving Scale

The PACS is a five-item self-administered instrument for assessing craving (Flannery et al-1999). Frequency, intensity, and duration of thoughts about drinking are assessed along with ability to resist drinking. The final item asks the responder to provide an average rating of his/her craving over the course of the past week. The questions on the PACS use descriptors coupled with numerical ratings ranging from 0 to 6. This CRF will be used as the source document.

11.24. Pittsburg Sleep Quality Index (PSQI)

The PSQI is a 19-item questionnaire with 6 subscales (subjective sleep quality, sleep latency, sleep duration, habitual sleep disturbances, use of sleep medication and day time dysfunction) (Buysse et al-1989). Each subscale is rated from 0 to 3 with the higher scores reflecting more severe sleep complaints. The addition of all the scores permits an analysis of the subject’s overall sleep experience in the past 30 days. The lower the overall score, the better the person sleeps. The tool has an adequate internal reliability, validity and consistency for clinical and community samples of the various populations. This questionnaire will be completed by the subject and will be both the source and CRF.

11.25. Pregnancy Test and Birth Control Record

An FDA approved rapid result urine pregnancy test will be used (i.e., dipstick test), unless the site IRB requires a blood-based assay. If applicable, subjects will be asked to sign a release of information form for study personnel to access medical records to obtain information regarding the outcome of a pregnancy that occurred during the study.

The birth control assessment is designed to determine a female subject’s compliance with the birth control specifications detailed in the inclusion criteria.

11.26. Prior and Concomitant Medications

All medications taken by the subject 2-months prior to the start of screening, during the screening period, and through the final follow-up contact will be recorded. All medications reported by the subject will be recorded on a source document and CRF.

11.27. Procedures for Monitoring Subject Compliance/Drug Accountability

Drug accountability will be performed by recording the number of capsules dispensed and the number of capsules returned at clinic visits. The amount dispensed, daily dose prescribed, and amount returned will be reconciled and recorded at each visit. The drug card will be reviewed for subject reported consumption of investigational product. If the subject reports missing capsules that were not taken, these data will also be recorded and used to calculate total drug exposure. If the investigational product blister card was not returned, then the subject's self-report of drug taken will be reported. If the study drug was discontinued, the reason for discontinuation will also be recorded.

11.28. Profile of Mood State (POMS)

The POMS measures dimensions of affect or mood ([McNair and Heuchert-2005](#)). It consists of 65 adjectives to which the subject responds according to a 5-point scale ranging from “not at all” to “extremely.” Six subscale scores will be computed for items grouped as follows: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion=Bewilderment. A total mood disturbance score will also be computed which consists of the sum of the 5 of the six subscale scores (the Vigor-Activity score is not included). This questionnaire will be completed by the subject and will be both the source and CRF.

11.29. Physical Examination

A physical examination of the oral cavity, head, eyes, ears, nose, and throat, cardiovascular system, lungs, abdomen, extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during screening. The physical exam will be updated on the day planned for randomization by querying the subject about any physical changes since the screening examination. Weight (kg) will be also be collected.

11.30. Mood, Behavior/Thinking, Suicidality, and Increased Intoxicating Effects of Alcohol

Neuropsychiatric symptoms related to suicidality, mood, and behavior/thinking will be assessed every week at the clinic or via telephone. The mood and behavior/thinking questions have been adapted from the Brief Psychiatric Rating Scale. Mood and behavior/thinking changes will be assessed by focused questions.

The mood questions are:

1. How has your mood been since we last talked?
 - a. In particular, have you or your family noticed that you are more hostile?
 - b. Have you or your family noticed that you are more easily agitated?
 - c. Have you or your family noticed that you are depressed?

The behavior/thinking questions are:

Since we last talked:

1. Have you or your family noticed any unusual changes in your behavior or thinking?
2. Have you been hearing voices or seeing things that others do not hear or see?
3. Have you had any thoughts about harming anyone?
4. Have you come to believe that people are spying on you, or that someone is plotting against you, or trying to hurt you?

NOTE: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.

An answer of Yes to any of the above questions requires physician notification and evaluation, notation in the progress notes. If the physician determines this is an AE, an AE CRF should be completed.

11.31. Screen Failures Documentation

To document the reason that a subject who consented to the study was not randomized, an Eligibility Checklist CRFs will be completed for these subjects.

11.32. Self-Reported Habit Index

Self-report Habit index (SRHI) (Verplanken and Orbell, 2003) is a 12-item self-report that provides an index of the degree to which alcohol drinking is habitual based on features of habit and expressing identity. It may be used as a co-variate. This assessment will be completed by the subject and used as source and CRF.

11.33. Subject Disposition

A subject disposition CRF will be completed for all subjects who are randomized to the study and who are dispensed investigational product. This CRF will be used to record the following data as applicable: 1) completion status of the subject at the end of their participation and if they were discontinued early, and reason for early discontinuation.

Completion status is as follows:

1. Subject completed full study (i.e., telephone contact was made at the Weeks 9 follow-up).
2. Subject completed the full intervention phase of the study (i.e., subject came to Week 7 clinic visit).
3. Subject was withdrawn prior to the Week 7 visit (reasons for early withdrawal are to be specified).
4. If the subject discontinued study medications.

Even if the subject had investigational product suspended for any reason but attended clinic visits, the above definitions still apply.

In addition, if the subject was confined and/or incarcerated at any time during the study, the dates of confinement and/or incarceration will be collected.

11.34. TLFB Interview

Drinking behavior will be assessed using the TLFB methodology ([Sobell & Sobell-1992](#)). The TLFB is a semi-structured interview that provides estimates of the daily quantity of alcohol consumption during specified time periods. It uses a calendar prompt and a number of other memory aids (e.g., holidays, payday, and other personally relevant dates) to facilitate accurate recall of drinking or other drug use during the target period. The procedure has been widely used in clinical and research contexts. It has demonstrated adequate levels of reliability and validity when administered as an in-person interview, over the telephone, and when administered via computer ([Carey-1997](#), [Sobell et al-1988](#), [Sobell et al-1996](#)). After consent is signed, the TLFB interview will be performed for the 28-day period prior to signing consent. Thereafter, the interview will be for the previous days between the last assessment and the day prior to the day of the assessment. It is estimated that a 28-day TLFB assessment will take 20 minutes to complete. In the event of missed visits, collection of missed drinking data at the following visit is required.

If a subject requests to withdraw from the study but agrees to continued telephone contact to assess drinking, the TLFB will be performed over the phone for the duration of the study at a frequency acceptable to the study subject and site staff.

An Excel spreadsheet customized for use in this study will be used for double data entry by clinical site staff to collect the TLFB drinking data. This spreadsheet contains a calculator to determine standard drink units (SDUs). This spreadsheet will be reviewed, compared with source documents and collected by study monitors for upload into the main study database.

Drinking days are defined as the number of days in which the subject reported any alcohol consumption (i.e., > 0 standard drinking units [SDUs]). A standard drink contains approximately 0.6 fluid ounces (oz) of pure alcohol. The data given by the subjects on amount and type of alcoholic beverage(s) consumed will be converted to SDUs. Standard drink unit definitions are provided in [Table 4](#).

Table 4: Standard Drink Unit Definitions

For Beer (~ 5% alcohol), the approximate number of SDUs in: <ul style="list-style-type: none">• 12 oz = 1.0• 16 oz = 1.3• 22 oz = 1.8• 40 oz = 3.3 For malt liquor (~ 7% alcohol), the approximate number of SDUs in: <ul style="list-style-type: none">• 12 oz = 1.4• 16 oz = 1.9• 22 oz = 2.6• 40 oz = 4.7
For table wine (~ 12% alcohol), the approximate number of SDUs in: <ul style="list-style-type: none">• 750 mL bottle = 25oz = 5.0• 5 oz glass = 1.0• 10 oz glass = 2.0
For 80 proof spirits (~ 40% alcohol), or hard liquor, the approximate number of SDUs in: <ul style="list-style-type: none">• 1.5 oz (mixed drink) = 1.0• 16 oz (pint) = 10.7• 25 oz (a fifth) = 16.7• 1.75 L (59 oz) = 39.3

11.35. Urine Drug Screen

An FDA cleared, CLIA waived urine drug test card will be used to assess candidates for recent use of opioids, cocaine, amphetamines, methamphetamine, THC, buprenorphine, methadone or benzodiazepines. During screening subjects must be negative for all substances except THC and in special cases opioids. If positive for opioids but recent opiate use for acute pain is reported by the subject, then the subject can be re-screened. If positive for these drugs at other times during the study, the subject will not be removed from the study but should be asked about medication use and possibly re-evaluate their medical history for substance abuse.

11.36. Varenicline Plasma Levels

Blood samples for determining plasma levels of varenicline will be collected at Weeks 3 and 7 to for medication compliance. If the blood collection is missed at Weeks 3 or 7, then the sample will be collected at the next blood draw (either visit make-up or Study Week 8). Blood will be collected in 6 mL Vacutainer™ tubes containing K₂-EDTA anticoagulant. Plasma will be collected after centrifugation and two aliquots of each subject's plasma will be stored at -20°C until the completion of the study. One aliquot of each replicate plasma sample will be shipped on dry ice to the testing lab at the end of the study for analysis.

11.37. Vital Signs

Vital signs to be assessed include sitting blood pressure and pulse rate (after sitting for at least 3 minutes).

12. Statistical Methods and Determination of Sample Size

12.1. Statistical Hypotheses

Primary Efficacy Endpoint: Subjects treated with varenicline will report significantly lower VAS craving ratings in response to *in vivo* alcohol cues during human lab testing than placebo-treated subjects.

Secondary Efficacy Endpoints: It is hypothesized that, during the last 4 weeks of the maintenance phase of treatment, the varenicline group, as compared to the placebo group, will:

1. Increase the percentage of subjects with no heavy drinking days. A “heavy drinking day” is 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men.
2. Increase the percentage of subjects abstinent from alcohol
3. Increase the percentage of subjects with at least a WHO 2-level decrease in alcohol consumption
4. Increase the percentage of subjects with at least a WHO 1-level decrease in alcohol consumption
5. Increase the percentage of days abstinent per week
6. Decrease the percentage of heavy drinking days per week
7. Decrease the percentage of very heavy drinking days per week
8. Decrease the weekly mean number of drinks per week
9. Decrease the weekly mean drinks per drinking day
10. Decrease the weekly mean cigarettes smoked per week among smokers
11. Increase the percentage of subjects abstinent from nicotine use among subjects who used any nicotine products in the week before randomization
12. Decrease the mean alcohol craving score (PACS)
13. Decrease the mean PSQI score
14. Decrease total mood disturbance (POMS)

12.2. Analysis Populations

The study analysis populations will consist of the following:

Modified Intention-to-Treat (mITT) Analysis Set: The mITT set is defined as subjects randomized to participate in the study that took at least one dose of investigational product and had at least one non-missing VAS craving primary endpoint (completed human laboratory assessment).

Evaluable Analysis Set: The evaluable analysis set for the secondary endpoints is defined as those subjects randomized to the study who took at least 1.5 mg per day for at least 80% of days in Weeks 2-6. All evaluable analysis sets will exclude subjects with a major protocol deviation.

Safety Analysis Set: The safety analysis set includes all subjects who received at least one dose of investigational product.

Both the primary and secondary efficacy analyses will use the mITT and the secondary efficacy analysis will use the evaluable analysis set. Safety analyses will be conducted on the safety analysis set.

12.3. General Approach

For descriptive purposes, dichotomous and categorical variables will be presented as number of observations and percentages; continuous variables will be given as means, standard deviations (SD), median, minimum (min) and maximum (max). Statistical tests will be two-tailed at a 0.05 Type I error rate. P-values for the primary and secondary endpoints of < 0.05 will be considered statistically significant. If large baseline differences are found between the treatment groups, we may elect to introduce covariates into the primary analyses, or in secondary analyses, to obviate the likelihood that conclusions may be affected by sample bias. Endpoint data will also be screened for outliers and skewness. Appropriate non-parametric tests will be used to compare treatment groups on continuous baseline characteristics that are not normally distributed. Continuous endpoint data that are not normally distributed will be transformed. Cohen's d will be used to calculate the effect size for means and Cohen's h will be used to calculate the effect size for proportions. Odds ratios will be provided for all dichotomous outcomes.

12.3.1. Analysis Addressing the Primary Efficacy Endpoint

Repeated-measures mixed effects models will be used to examine drug-placebo differences in VAS craving ratings in response to beverage exposure, where drug is treated as a fixed, between-subjects variable and beverage presentation is the repeated measure. Beverage will be considered a fixed, within-subjects variable and subject as a random effect.

12.3.2. Secondary Efficacy Endpoints Analysis

Continuous secondary endpoints (percent heavy drinking days, percent very heavy drinking days, percent days abstinent, drinks per week, drinks per drinking day, number of cigarettes smoked per week, PACS, POMS, and PSQI score) will be analyzed using a mixed-model repeated measures ANCOVA controlling for site, nicotine use in the week before randomization, and baseline drinking as fixed factors. Models will also include time by treatment group interaction term. Additional covariates may be included that are significantly correlated with outcome and/or if there are differences across the treatment groups.

Analysis of the dichotomous secondary endpoints (percentage subjects with no heavy drinking days, percentage subjects abstinent from alcohol, percentage of subjects achieving at least a one and two-level shift in WHO alcohol consumption, and no nicotine use during the last 4-weeks of the maintenance period among subjects who used in the week prior to randomization) will be conducted via logistic regression. Covariates may be included provided there are a sufficient number of events.

In general, no imputation for missing endpoint data will be performed. However, as a sensitivity analysis, missing drinking data for the secondary endpoint percent heavy drinking days will be handled in two ways as done by [Litten et al \(2013\)](#): (a) by imputing missing data as heavy drinking days and (b) by using multiple imputation. The multiple imputation model will the same

covariates as the efficacy model for this endpoint. Twenty-five iterations of this model will be run, and model estimates will be averaged using PROC MIANALYZE in SAS, or a similar procedure.

12.4. Safety Outcomes

AEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, and class (SOC) designation. The severity, frequency, and relationship of AEs to investigational product will be presented by preferred term by SOC grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on preferred terminology) will be counted once only for a given study participant. If the same AE occurred on multiple occasions, the highest severity will be assumed. Thus, study participants are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE. Laboratory data, pregnancy test results, and alcohol breathalyzer results, psychiatric symptoms, and CIWA scores will be reported as summary statistics. The numbers and proportion of subjects who reported CIWA scores ≥ 10 at any time after the start of dosing will be presented. ACQ-SF-R will be administered before and after exposure to alcohol and picture stimuli during the cue reactivity paradigm on the screening visit, study week 3 and study week 6 visit to ensure that subjects have returned to baseline levels.

12.5. Compliance and Participation Outcomes

Medication compliance is defined as the amount of medication taken as a proportion of the total amount prescribed. Compliance will also be evaluated by determining the proportion of subjects who were prescribed varenicline, reported taking varenicline, and had a plasma sample with detectable varenicline. The participation rate is the percentage of subjects with complete drinking data. Compliance and participation rates will be reported on a weekly basis and across the entire trial duration.

12.6. Randomization Plan/Control of Bias

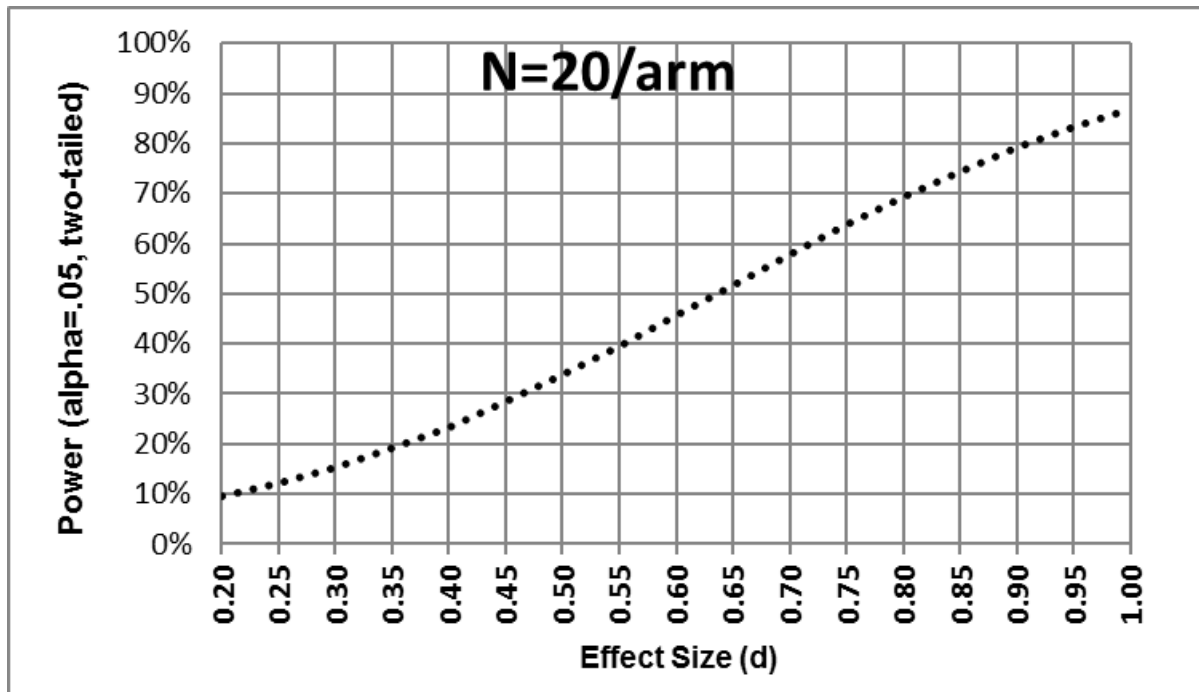
Permuted blocked random allocation of subjects to study groups will be used to balance groups with respect to nicotine use versus no use in the week before randomization. Nicotine use was selected since regular smokers may potentially derive more or less benefit from study medication and by virtue of the high correlation between smoking and alcohol behaviors.

12.7. Determination of Sample Size

The sample size for the primary endpoint was based on a human laboratory study of varenicline reported by [McKee et al \(2009\)](#) that found an effect size for VAS craving (Cohen's $d=0.95$). This effect size is consistent with those derived from other human laboratory studies that used a similar experimental paradigm as the present study, but evaluated different medications: mifepristone ($d=1.25$) ([Vendruscolo et al-2015](#)) and gabapentin ($d=1.00$) ([Mason et al-2009](#)). With an intake sample of 48 subjects (24 per arm) and 16% attrition, it is projected that the sample size for primary outcome analyses will be 40 (20 per arm). The alpha level for the primary analyses will be 0.05, two-tailed. The conservative effect size estimate is $d=.95$, per [McKee et al \(2009\)](#). Equal variances in both groups are assumed. These assumptions lead to a projected power of 83%.

The Figure below represents the power for different effect sizes using a two-sided alpha of 0.05 with an effective n of 40 subjects (20 per arm).

Figure 1: Power Analysis for Sample Size Estimation



13. Quality Control and Quality Assurance

This study will be conducted under International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use; the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor's representatives (clinical monitors). Clinical monitors will review source documents and CRFs for accuracy and completeness during on-site monitoring visits; any discrepancies will be resolved with the investigator, as appropriate.

Significant and/or repeated noncompliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in study site termination and regulatory authority notification.

13.1. Study Monitoring

Study monitoring will be the responsibility of designated clinical monitors of NIAAA. Monitors will assure compliance with the clinical protocol and ICH GCPs, human subject's protection, drug accountability, maintenance of the site regulatory file, and conformance of CRF data with source documents. Monitoring visits by clinical monitors will be scheduled to take place at the initiation of the study, during the study at appropriate intervals, and after the last subject has completed the study. A report of monitoring observations will be provided to the PI (for corrective actions) and the Sponsor.

13.2. Audits and Inspections

Authorized representatives of the Sponsor and the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines, and any applicable regulatory requirements.

The PI should contact NIAAA if contacted by a regulatory agency about an inspection.

14. Ethics

14.1. Ethics Review

The study will be conducted under a protocol reviewed by the local site's IRB; the study is to be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 Code of Federal Regulations (CFR) Part 50 and the Belmont Principles.

14.1.1. Review/Approval of Study Protocol

The site must obtain written approval from the appropriate IRB to conduct the study before study initiation. NIAAA will issue a formal authorization letter for the study to be initiated at the site. Progress reports will be submitted to the IRB by the Investigator at the frequency requested by the site's IRB.

14.1.2. Protocol Modifications

All necessary protocol changes will be submitted in writing as protocol amendments to the IRB by the site PI for approval prior to implementation.

14.1.3. Protocol Deviation Reporting Procedures

All subject-specific deviations from the protocol are to be documented. The PI or designee will be responsible for identifying and reporting all deviations, which are occurrences involving a procedure that did not follow the study protocol. Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study is considered a major deviation and will be reported immediately to the NIAAA Project Manager and the local site's IRB.

14.2. Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP Guideline and the Code of Federal Regulations (CFR).

14.2.1. Confidentiality

14.2.1.1. Confidentiality of Data

By signing this protocol the investigator affirms to NIAAA that information furnished to the investigator by NIAAA will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

14.2.1.2. Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff, NIAAA program officials, and NIAAA clinical monitors will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by representatives of NIAAA. Upon approval of the study by an IRB, an application will be filed with NIAAA for a Certificate of Confidentiality.

By signing the protocol, the investigator agrees that within local regulatory restrictions and ethical considerations, NIAAA or any regulatory agency may consult and/or copy study documents in order to verify CRF data.

14.2.2. Compensation for Participation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of cash or vouchers. Compensation will be provided in increasing amounts with each subject visit and is detailed in the informed consent form.

14.2.3. Written Informed Consent

The informed consent process and document will be reviewed and approved by the IRB and sponsor's representative prior to initiation of the study. The consent document contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR Part 50. The consent document indicates that by signature, the subject, permits access to relevant medical records by NIAAA or designated clinical monitors.

A written informed consent document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles, and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for each subject.

All potential subjects for the study will be given a current copy of the Informed Consent Form to read. All aspects of the study and informed consent will be explained in lay language to the subject by either the investigator, or a medically trained designee. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation.

All study subjects will be given a copy of the signed informed consent.

14.2.4. Delegation of Responsibilities and Adequate Resources

The PI should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term “investigator” used throughout this protocol refers to the PI and/or qualified subinvestigators. The PI may delegate responsibilities to other study site personnel. The PI shall delegate tasks only to individuals qualified by education, training, and experience to perform the delegated tasks. The PI shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The PI is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log

identifying all delegated duties and the individual to whom they have been delegated will be maintained at the study site.

15. Data Handling and Record Keeping

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, laboratory results, data recorded in automated instruments, and pharmacy records, etc. Data will be transcribed from source documentation into paper CRFs. Only questionnaire data will be entered directly onto CRF (i.e., without prior written or electronic record of data). The transcribed data will be consistent with the source documents or the discrepancies will be explained.

Clinical monitors will review all source records and compare them to the data entered onto the CRF. All entries, corrections, and alterations will be made by the investigator or other authorized study personnel. Any errors identified during monitoring will have a query posted by monitor for site staff to address.

15.1. Subject Identification and Confidentiality

Subjects will be identified on CRFs by a unique subject number. No personal identifier will be used in any publication or communication used to support this research study. The subject number will be used if it becomes necessary to identify data specific to a single subject. The Sponsor's representative and designated clinical monitors of NIAAA and the IRB are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied or electronic medical and research records.

15.2. Inspection of Records

The sponsor's representative or designee will be allowed to visit the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, investigational product stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

Subjects' health information is used to report results of research to the sponsor's representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. The consent document indicates that by signature, the subject permits access to relevant medical records by NIAAA and NIAAA's representatives.

Upon a subject's termination from the trial, completed CRFs will be ready and available for on-site review by the sponsor's representative at scheduled monitoring visits.

15.3. Retention of Records

The investigator is responsible for creating and/or maintaining all study documentation required by ICH E6 section 8, as well as any other documentation defined in the protocol. The investigator must provide key documents to the Sponsor prior to start of the study.

Investigators are required to retain a copy of all regulatory documents and records that support the data for this study for 2 years following study completion.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the

responsibility. NIAAA must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

15.4. Trial Registration

NIAAA has registered the trial on the National Library of Medicine's Clinical Trials Registry on the world wide web at <http://www.clinicaltrials.gov>.

16. Protocol Signature Page

NIAAA REPRESENTATIVES

Typed Name	Signature	Date
<u>Raye Z. Litten, Ph.D.</u> NIAAA Principal Investigator	_____	_____
<u>Joanne Fertig, Ph.D.</u> NIAAA Investigator	_____	_____
<u>Daniel E. Falk, Ph.D.</u> NIAAA Investigator	_____	_____
<u>Megan Ryan, MBA, CCRP</u> NIAAA Project Manager	_____	_____
<u>Lorenzo Leggio, M.D., Ph.D., M.Sc.</u> Medical Monitor	_____	_____

INVESTIGATORS

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 11.2.7 of this protocol.

Typed Name	Signature	Date
_____	_____	_____
_____	_____	_____

17. References

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